Toxicity Assessment of Concurrent Gabapentin/Pregabalin Administration with High-Dose Melphalan in Autologous Hematopoietic Cell Transplant Recipients

Jonathan Angus
Seattle Children's Hospital
Aaron Cumpston
WVU Medicine
Lauren Veltri
WVU Medicine
Kelly Ross
WVU Medicine
Sijin Wen
West Virginia University
Megan Dillaman (bodgem@wvumedicine.org)
WVU Medicine https://orcid.org/0000-0002-8234-7598

Research Article

Keywords: Gabapentin, pregabalin, melphalan, autologous hematopoietic cell transplant, myeloma, nausea, vomiting, mucositis, neuropathy

Posted Date: May 14th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-449908/v1

Abstract

Peripheral neuropathy is a common toxicity of various multiple myeloma regimens. A theoretical pharmacokinetic interaction mediated through L-amino acid transporter 1 and 2 exists between gabapentin (GP) and pregabalin (PG) with melphalan. Therefore, it is likely concurrent administration of either GP or PG will occur in patients receiving high-dose melphalan (HD-Mel) conditioning for autologous hematopoietic cell transplantation, which could potentially increase cellular uptake and worsen mucosal injury. A retrospective chart review of adult patients from January 2012 to July 2016 who received HD-Mel (140-200mg/m^2) at West Virginia University Medicine was performed to assess toxicity and outcomes in these patients. A total of 80 patients were included in the study, with 30 patients receiving GP or PG and 50 control patients. There were no significant differences in grade 2 or higher mucositis, admissions for nausea/vomiting/diarrhea, intravenous opioid requirements, oral topical therapies, antidiarrheal medication use, rescue antiemetics, days of nausea or vomiting, pain scores, neutrophil or platelet engraftment, treatment-related mortality, progression-free survival, or overall survival. Our data suggest that it is safe to continue GP/PG therapy throughout HD-Mel therapy, with no negative transplant outcomes. Prospective studies or evaluation of larger databases are necessary to better characterize the clinical effect of concomitant therapy.

Introduction

L-type amino acid transporter 1 (LAT1) and 2 (LAT2) are responsible for the transportation of large neutral amino acids across the intracellular membrane. These transporters appear to have specific drug-carrying functionality with certain medications, which are structurally similar to amino acids, such as gabapentin (GP), pregabalin (PG), melphalan, levodopa, methyldopa, and baclofen.[1,] LAT1 is primarily found in the brain, placenta, certain tumors, and it may also play a role in transport of molecules into growing cells. LAT2 is primarily found in the kidney, colon, intestine, and may be responsible for basolateral efflux of molecules (transport in the direction of lumen to extracellular fluid).[1] LAT1 overexpression has been documented in various malignancies and is thought to aid in tumor growth, migration, and invasion. In cell-line pharmacokinetic studies, GP significantly inhibited the uptake of amino acids by LAT1 and LAT2. GP transport into cells has previously been demonstrated to be inhibited by the amino acid L-phenylalanine.[2]

Melphalan, a phenylalanine derivative of nitrogen mustard, is an alkylating antineoplastic agent used at high doses as a conditioning agent prior to autologous hematopoietic cell transplantation (auto-HCT) primarily in patients with multiple myeloma. High-dose melphalan (HD-Mel) is associated with significant toxicity including oral mucositis, nausea, vomiting, and diarrhea.[4] Toxicities can be severe enough to warrant inpatient admission which may increase treatment costs, burden the health-care system, decrease patient satisfaction, and compromise patient outcomes. Pharmacokinetic analysis of the interpatient variability in melphalan sensitivity has identified pretreatment hematocrit, fat-free mass, and estimated creatinine clearance as potential sources of this disparity.[,] Uptake of melphalan into cells is

primarily mediated by LAT1 and LAT2, which are encoded by the solute carrier family 7 member 5 (SLC7A5) and solute carrier family 7 member 8 (SLC7A8) genes, respectively. A single nucleotide polymorphism in SLC7A5 (rs4240803) has been shown to have a significant effect on melphalan distribution within the peripheral compartment.[7] SLC7A5 is responsible for melphalan uptake into cells and polymorphisms have previously been shown to be associated with increased toxicity following HD-Mel.[7]

Chemotherapy-induced peripheral neuropathy is a common toxicity of various multiple myeloma treatment options. GP and PG are anticonvulsant medications useful in the treatment of neuropathic pain due to their ability to bind the neuronal α-2/δ subunits of voltage-gated calcium channels and decrease transmission of afferent pain signals. It is likely concurrent administration of either GP or PG will occur in patients receiving HD-Mel conditioning for auto-HCT, which could theoretically result in changes in cellular uptake, affect mucosal injury, and contribute to other HD-Mel toxicities.[8] To our knowledge, there are no published studies evaluating possible interactions of GP or PG with HD-Mel, their effect on toxicities, and impact on clinical outcomes. A retrospective study of patients receiving these concomitant medications, which may alter LAT1/LAT2 transport, was therefore undertaken to compare outcomes versus a cohort of patients not receiving GP or PG.

Materials And Methods

Design

A retrospective review of consecutive patients with multiple myeloma undergoing outpatient auto-HCT and conditioning with single agent HD-Mel at West Virginia University Hospitals from January 2012 to July 2016 was conducted. This study was approved by the institutional review board at West Virginia University Hospitals. The purpose of this study was to determine if patients receiving concomitant GP or PG had different toxicities and outcomes with HD-Mel compared to patients who were not receiving any additional medication known to interact with LAT1/LAT2.

Patient Population

Patients aged ≥ 18 receiving an outpatient auto-HCT with a melphalan dose of ≥ 140 mg/m^2 were included. Exclusion criteria included concomitant use of levodopa, methyldopa, or baclofen; and deviation from institutional standard anti-emetic regimen of steroids, ondansetron, and fosaprepitant. For mucositis prophylaxis, patients at our institution are offered cryotherapy for 60 minutes surrounding melphalan infusion.

Outcome Measures

The primary endpoint was rate of mucositis of any grade documented in patients receiving concomitant GP/PG compared to patients not receiving either medication. The secondary endpoints included hospital admission rate, total parenteral nutrition (TPN) utilization, patient-controlled analgesia initiation,

intravenous opioid requirements prior to engraftment (in oral morphine equivalents), use of topical mucosal agents (e.g. lidocaine, ketamine), use of antidiarrheal agents (e.g. atropine/diphenoxylate, loperamide), use of rescue anti-emetics, number of days of nausea documented prior to neutrophil engraftment, number of days of vomiting documented prior to neutrophil engraftment, median daily pain scores, time to neutrophil engraftment, time to platelet-20 engraftment, time to platelet-50 engraftment, 30-day treatment-related mortality (TRM), 100-day TRM, progression-free survival (PFS), and overall survival (OS).

Study Definitions

Use of topical mucosal agents, use of antidiarrheal agents, and use of rescue anti-emetics were defined as and captured by tracking of breakthrough medication orders placed on clinic encounters, inpatient encounters if admitted, and prescriptions sent during the post-transplant period. Topical mucosal agents and antidiarrheal agents were not standardly prescribed in advance of transplant. Ondansetron and prochlorperazine prescriptions were standardly given to all patients prior to start of conditioning, and only included if additional supply was needed. Mucositis was graded according to the Common Terminology Criteria for Adverse Events criteria. Neutrophil engraftment was defined as the first of 3 consecutive days to an absolute neutrophil count of > 500 cell/μL after post-transplantation nadir. Platelet-20 and platelet-50 engraftment were defined as the first of 7 consecutive days to platelet count above 20,000 or 50,000 cells/μL, respectively, without platelet transfusion. TRM for the 30- and 100-day benchmarks were assessed in all patients and were defined as death from any cause other than disease progression.

Statistical Analysis

Descriptive statistics were used for baseline patient characteristics. For continuous variables, such as age, the Wilcoxon rank test was used to assess statistical significance by comparing the whole distribution between the treated and untreated groups without assuming a normal distribution (i.e. distribution free). For binomial categorical variables such as gender, the gender distribution (%) was compared between treated and untreated groups using Fisher’s exact test. For categorical variables with 3 or more levels such as performance status (PS 0 or 1 or 2), the distribution (%) across all three levels was compared between treated and untreated groups also using Fisher’s exact test.

Results

Eighty patients met criteria for study inclusion. Baseline demographics are listed in Table 1. Thirty patients received concomitant GP/PG and 50 control patients did not receive any LAT1/LAT2 transported medications in addition to melphalan. There were no significant differences in baseline characteristics between the two groups.

Table 1
Patient demographics

Demographic		GP or PG (n = 30)	GP or PG Untreated (n = 50)	P-value
Age (y), median (range)		60 (34–70)	60 (39–74)	0.854
Male Gender, n (%)		21 (70)	27 (54)	0.238
BMI (kg/m^2), median (range)		32 (20.8–46.6)	28.9 (20.6–43.9)	0.062
Pre-Transplant Serum Creatinine (mg/dL), median (range)		0.97 (0.68–1.7)	0.93 (0.58–2.63)	0.758
Melphalan Dose 140 mg/m^2, n (%)		5 (17)	9 (18)	0.999
Melphalan Dose 200 mg/m^2, n (%)		25 (83)	41 (82)	0.999
ECOG-PS 0–1 at Transplant, n (%)		26 (87)	41 (82)	0.757
KPS, median (range)		80 (60–100)	80 (50–100)	0.269
≥ VGPR Pre-Transplant, n (%)		14 (47)	17 (34)	0.344
HCT-CI < 3, n (%)		26 (86.7)	36 (72)	0.712
Cell Dose (CD34 + cells x10e^6/kg), median (range)		4.4 (2.1–9.8)	4.5 (1.5–9.8)	0.515
Mayo Clinic Myeloma Risk Category[15], n (%)	Standard	12 (40)	16 (32)	0.714
	Intermediate	4 (13.3)	7 (14)	
	High	5 (16.7)	6 (12)	
	Unknown	9 (30)	21 (42)	

Abbreviations:

BMI - body mass index, ECOG-PS - Eastern Cooperative Oncology Group Performance Status, KPS - Karnofsky Performance Status, VGPR - Very Good Partial Response, HCT-CI - Hematopoietic Cell Transplantation-Comorbidity Index

Analysis of the primary endpoint demonstrated there was no significant difference in rates of mucositis. The rates of mucositis between the treated and untreated groups were 59% vs. 52% for grade 1, 24% vs. 19% for grade 2, 7% vs. 10% for grade 3, and 10% vs. 19% with no mucositis (p = 0.833) in the GP/PG group vs. the control group, respectively.

Secondary endpoints showed no significant difference between the two groups. The percentage of patients developing ≥ grade 2 mucositis was 30% in the GP/PG treated group compared with 40% in the control group (p = 0.473). Admission rate for nausea/vomiting/diarrhea was found to be to be 10% in the GP/PG treated group compared with 18% in the control group (p = 0.439). Overall, parenteral nutrition utilization was low with no patients in the GP/PG treated group and one patient (2%) in the untreated group requiring TPN (p = 0.999). Patient-controlled analgesia usage followed a similar trend with no patients in the GP/PG treated group and one patient (2%) in the untreated group utilizing a PCA (p = 0.999). Average intravenous opioid requirements prior to engraftment were similar at 11.2 mg in the PG/PG treated group and 13 mg in the control group (p = 0.849). Use of topical mucosal agents did not significantly differ between groups with 27% of patients in the GP/PG treated group and 28% of patients in the untreated group requiring use (p = 0.999). Antidiarrheal agent use between the two groups was not significantly different between groups with 63% in the GP/PG treated group and 66% in the control group (p = 0.814). Percent of patients requiring the use of rescue anti-emetics was similar between the two groups at 80% and 78%, respectively; the median number of rescue anti-emetic doses administered was two in the GP/PG treated group compared with four in the control group (p = 0.999). The median number of days of nausea and of vomiting documented prior to neutrophil engraftment were 3.5 and 0 vs. 4 and 0 days, respectively (p = 0.572 and p = 0.481). Median daily pain scores were similar in the GP/PG treated group (2 out of 10) to the untreated group (1.25 out of 10, p = 0.733). Median time to neutrophil engraftment (12 vs 12 days, p = 0.511), median time to platelet-20 engraftment (15.5 vs 15, p = 0.156), and median time to platelet-50 engraftment (18 vs 19, p = 0.532) were not significantly different between treatment groups. Of note, no patients in the GP/PG treated group and 6% (n = 3) of patients in the untreated group experienced TRM within 100 days (p = 0.288), with similar median PFS and OS at 694 vs. 720 days and 906 vs. 993 days, respectively (p = 0.540 and p = 0.58) (Figs. 1 and 2).

When the primary and secondary outcomes were stratified by the dose of GP or PG, there were no statistically significant differences between the high-dose group and the low-dose group (Table 2). Low-dose GP/PG was defined as ≤ 900 mg per day and ≤ 150 mg per day, respectively. High dose was defined as the converse. Seventeen patients were defined as low-dose and 13 patients were defined as high-dose.

Table 2
Outcomes Stratified by Gabapentin/Pregabalin Dose

Result	Low-Dose GP/PG[1] Median or % (range); P-Value (n = 17)	High-Dose GP/PG Median or % (range); P-Value (n = 13)	Untreated Median or % (range) (n = 50)
Highest Severity of Mucositis	1 (0–3); p = 0.285	1 (0–3); p = 0.066	1 (1–3)
Days of Nausea	4 (2–11); p = 0.184	3 (1–8); p = 0.555	4 (0–16)
Days of Vomiting	0 (0–4); p = 0.719	0 (0–3); p = 0.502	0 (0–7)
Oral Morphine Equivalents (mg)	0 (0–66); p = 0.424	0 (0-228); p = 0.726	0 (0-177)
Use of Topical Agent	35.3%; p = 0.558	15.4%; p = 0.486	28%
Rescue Anti-Emetic Use	82.4%; p = 1.0	77%; p = 1.0	78%
Number of IV Anti-Emetic Rescue Doses	2 (0–41); p = 0.826	2 (0–22); p = 0.204	4 (0–67)
Repeat Fosaprepitant Administration	17.6%; p = 1.0	0%; p = 0.184	18%
Olanzapine Administration	11.8%; p = 0.595	0%; p = 1.0	6%
Daily Pain Scores (0–10)	0 (0–8); p = 0.992	4 (0–9); p = 0.465	1 (0–9)
Antidiarrheal Administration	70.6%; p = 0.775	53.8%; p = 0.522	66%
Time to Neutrophil Engraftment (days)	12 (11–18); p = 0.944	12 (11–14); p = 0.441	12 (10–20)
Time to Plt-20 Engraftment (days)	16 (12–25); p = 0.131	15 (12–26); p = 0271	13.5 (11–31)
Time to Plt-50 Engraftment (days)	19 (14–28); p = 0.478	18 (12–35); p = 0.826	18 (13–35)
Progression Free Survival (days)	706 (188–1769); p = 0.920	537 (76-1748); p = 0.596	720 (14-1898)

Abbreviations: Plt-20 - Time to reach a transfusion independent platelet level of 20,000, Plt-50 - Time to reach a transfusion independent platelet level of 50,000, TRM - Treatment Related Mortality

[1] Low-dose GP/PG was defined as ≤ 900 mg per day and ≤ 150 mg per day, respectively.

Result	Low-Dose GP/PG[1] Median or % (range); P-Value (n = 17)	High-Dose GP/PG Median or % (range); P-Value (n = 13)	Untreated Median or % (range) (n = 50)
Overall Survival (days)	941 (451–1769); p = 0.575	871 (83-1748); p = 0.412	992.5 (14-1898)
30-Day TRM	0%; p = 1.0	0%; p = 1.0	2%
100-Day TRM	0%; p = 0.565	0%; p = 1.0	6%
Abbreviations: Plt-20 - Time to reach a transfusion independent platelet level of 20,000, Plt-50 - Time to reach a transfusion independent platelet level of 50,000, TRM - Treatment Related Mortality			
[1] Low-dose GP/PG was defined as ≤ 900 mg per day and ≤ 150 mg per day, respectively.			

Discussion

This is the first study to our knowledge reviewing the clinical implications of the interaction between GP/PG and HD-Mel. There were no significant differences in primary or secondary outcomes between the two groups, and it appears to be safe to continue GP/PG therapy throughout auto-HCT with HD-Mel. While not significant, we observed a numerical decrease in mucositis, nausea, and vomiting in the GP/PG group. This effect is possibly related to a decrease in mucosal melphalan concentrations due to the interaction with LAT1/LAT2. Another proposed mechanism may be documented anti-emetic properties of GP and PG, with proven efficacy in the treatment of post-operative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting (CINV).[7] When the primary and secondary outcomes were stratified by the dose of GP or PG, there appeared to be a numerical reduction in the direction of higher doses correlating with lower incidence of mucositis, nausea, vomiting, and pain. These differences did not reach statistical significance, a larger GP/PG treated group cohort number may help to clarify the association between dose and outcome measures.

It has been shown that melphalan pharmacokinetics can vary by as much as 6-fold between patients based on various characteristics. A study by Kuhne et al sought to determine if LAT1 and LAT2 polymorphisms could account for this interpatient variability in exposure.[14] Although this study found no difference in kinetics based on LAT1 or LAT2 gene heterogeneity, there was almost no genetic variability in the protein coding regions, meaning most polymorphisms studied were in the intronic, or non-coding gene regions. The variability present in non-coding regions and the melphalan pharmacokinetic differences associated with LAT1 and LAT2 polymorphisms cannot be reliably explained by SNPs occurring in regions with proximity to the LAT1 and LAT2 gene expression promoter sequences because although numerous variants were found, there was no evidence for LAT1 and LAT2 genetic variants affecting the expression of these genes. Both LAT1 and LAT2 have a very low nucleotide diversity in the transporter protein coding region compared to other human genes, meaning they are functionally important genes. More recently, polymorphisms observed in SLC7A5 and SLC7A8, responsible for

encoding LAT1 and LAT2, have been associated with increased TPN dependence after HD-Mel administration, which suggests alterations in LAT1 and LAT2 transport confer significant differences in the degree of mucosal injury experienced by patients receiving HD-Mel.[7] Despite the pharmacokinetic interaction between GP/PG with melphalan, as well as the influence polymorphisms in LAT1 and LAT2 genes have on melphalan toxicity, the co-administration of GP/PG with melphalan during auto-HCT appears to be safe and may confer a protective effect in terms nausea, vomiting, and mucositis. The numerically lower PFS and OS seen in the high-dose GP/PG groups could be explained by the presence of relatively worse neuropathy in a more heavily pre-treated group. This could also be related to a decrease in anti-myeloma activity due to the interaction, and further studies should be done to evaluate this parameter.

Limitations of this study included the retrospective design which may have limited the ability to accurately report gastrointestinal adverse events, single center data, and the relatively small number of patients. SLC7A5 and SLC7A8 polymorphism testing was not completed for the patient cohort, although polymorphisms could have potentially impacted melphalan exposure. Patients who had not received fosaprepitant prior to HD-Mel were excluded; therefore, the total number of patients included in the analysis was limited to those from 2011 onwards when administration of fosaprepitant was made standard of care. A prospective observational arm of this study is currently planned in order to more rigorously collect data to assess incidence of mucositis, nausea, vomiting, diarrhea, and endpoints related to pain.

In conclusion, this study represents the first data exploring the clinical implications of a pharmacokinetic drug-drug interaction with the potential to impact morbidity and mortality in auto-HCT recipients. It appears safe to continue GP/PG therapy throughout HD-Mel therapy with no negative outcomes described at this time. Larger studies are necessary to better characterize the clinical implications of concomitant therapy.

Declarations

Funding: Not applicable

Conflicts of interest: The authors declare that they have no conflict of interest.

Authors' contributions: All authors have made substantial contributions to the conception/design of the project, data analysis and interpretation, and manuscript draft and review.

Ethics approval: This study was approved by the institutional review board at West Virginia University Hospitals.
Consent to participate: Not applicable – research was retrospective in nature.

Consent for publication: All authors grant final approval of the manuscript draft for publication.

Availability of data and material: All data and materials comply with standards.

Code availability: Not applicable

Acknowledgements: None

Funding: None

Competing Interests: None to declare

Supplementary data: None

References

[1] del Amo EM, Urtti A, Yliperttula M. Pharmacokinetic role of L-type amino acid transporters LAT1 and LAT2. *Eur J Pharm Sci.* 2008;35(3):161-174.

[2] Dickens D, Webb SD, Antonyuk S, Giannoudis A, Owen A, Rädisch S, Hasnain SS, *et al*. Transport of gabapentin by LAT1 (SLC7A5). *Biochem Pharmacol.* 2013;85(11):1672-1683.

[3] Shi L, Luo W, Huang W, Huang S, Huang G. Downregulation of L-type amino acid transporter 1 expression inhibits the growth, migration and invasion of gastric cancer cells. *Oncol Lett.* 2013;6(1):106-112.

[4] Patel M, Dalvi P, Gokulgandhi M, Kesh S, Kohli T, Pal D, Mitra AK. Functional characterization and molecular expression of large neutral amino acid transporter (LAT1) in human prostate cancer cells. *Int J Pharm*. 2013;443(1-2):245-253.

[5] Shah N, Callander N, Ganguly S, Gul Z, Hamadani M, Costa L, *et al*. Hematopoietic stem cell transplantation for multiple myeloma: Guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21(7):1155-1166.

[6] Nath CE, Shaw PJ, Montgomery K, Earl JW. Population pharmacokinetics of melphalan in paediatric blood or marrow transplant recipients. *Br J Clin Pharmacol.* 2007;64(2):151-164.

[7] Cho YK, Sborov DW, Lamprecht M, Li J, Wang J, Hade EM, *et al*. Associations of high-dose melphalan pharmacokinetics and outcomes in the setting of a randomized cryotherapy trial. *Clin Pharmacol Ther.* 2017;102(3): 511-519.

[8] Giglia J, White M, Hart A, Toro J, Freytes C, Holt C, *et al*. A single nucleotide polymorphism in SLC7A5 is associated with gastrointestinal toxicity after high-dose melphalan and autologous stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant.* 2014;20(7):1014-1020.

[9] Beijers AJ, Vreugdenhil G, Oerlemans S, Eurelings M, Minnema MC, Eeltink CM, *et al*. Chemotherapy-induced neuropathy in multiple myeloma: Influence on quality of life and development of a questionnaire

to compose common toxicity criteria grading for use in daily clinical practice. *Support Care Cancer.* 2016;24(6):2411-2420.

[10] Guttuso T, Jr. Gabapentin's anti-nausea and anti-emetic effects: A review. *Exp Brain Res.* 2014;232(8):2535-2539.

[11] National Cancer Institute. Common terminology criteria for adverse events (CTCAE), v4.03. 2010. National Cancer Institute, Bethesda, MD.

[12] Cruz FM, de Iracema Gomes Cubero D, Taranto P, Lerner T, Lera AT, da Costa Miranda M, *et al*. Gabapentin for the prevention of chemotherapy- induced nausea and vomiting: A pilot study. *Support Care Cancer*. 2012;20(3):601-606.

[13] Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg.* 2007;104(6):1545-1556.

[14] Kuhne A, Kaiser R, Schirmer M, Heider U, Muhlke S, Niere W, *et al*. Genetic polymorphisms in the amino acid transporters LAT1 and LAT2 in relation to the pharmacokinetics and side effects of melphalan. *Pharmacogenet Genomics.* 2007;17(7):505-517.

[15] Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: Updated mayo stratification of myeloma and risk-adapted therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013;88(4):360-376.

Figures

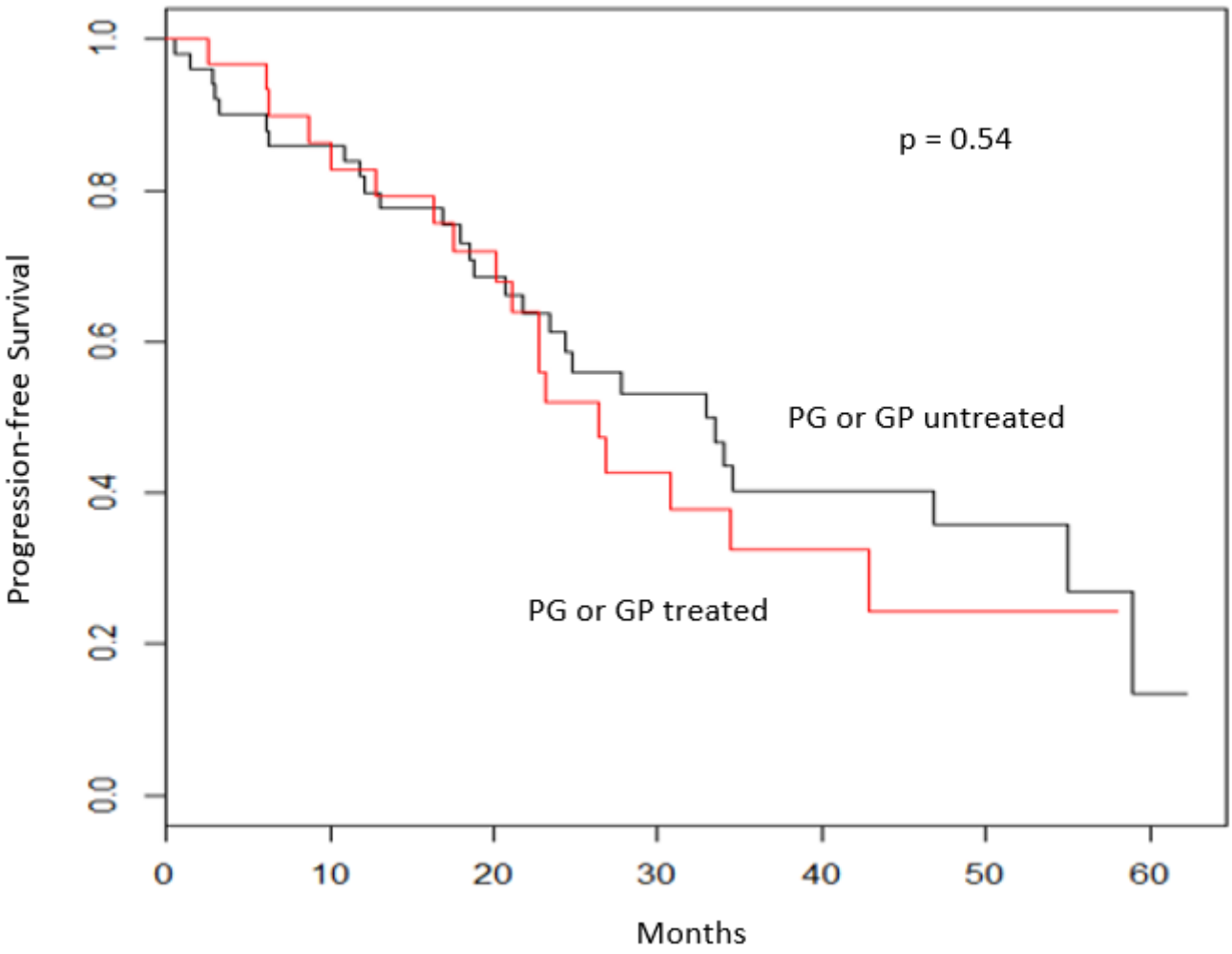

Figure 1

Kaplan-Meier Curve of Progression-Free Survival

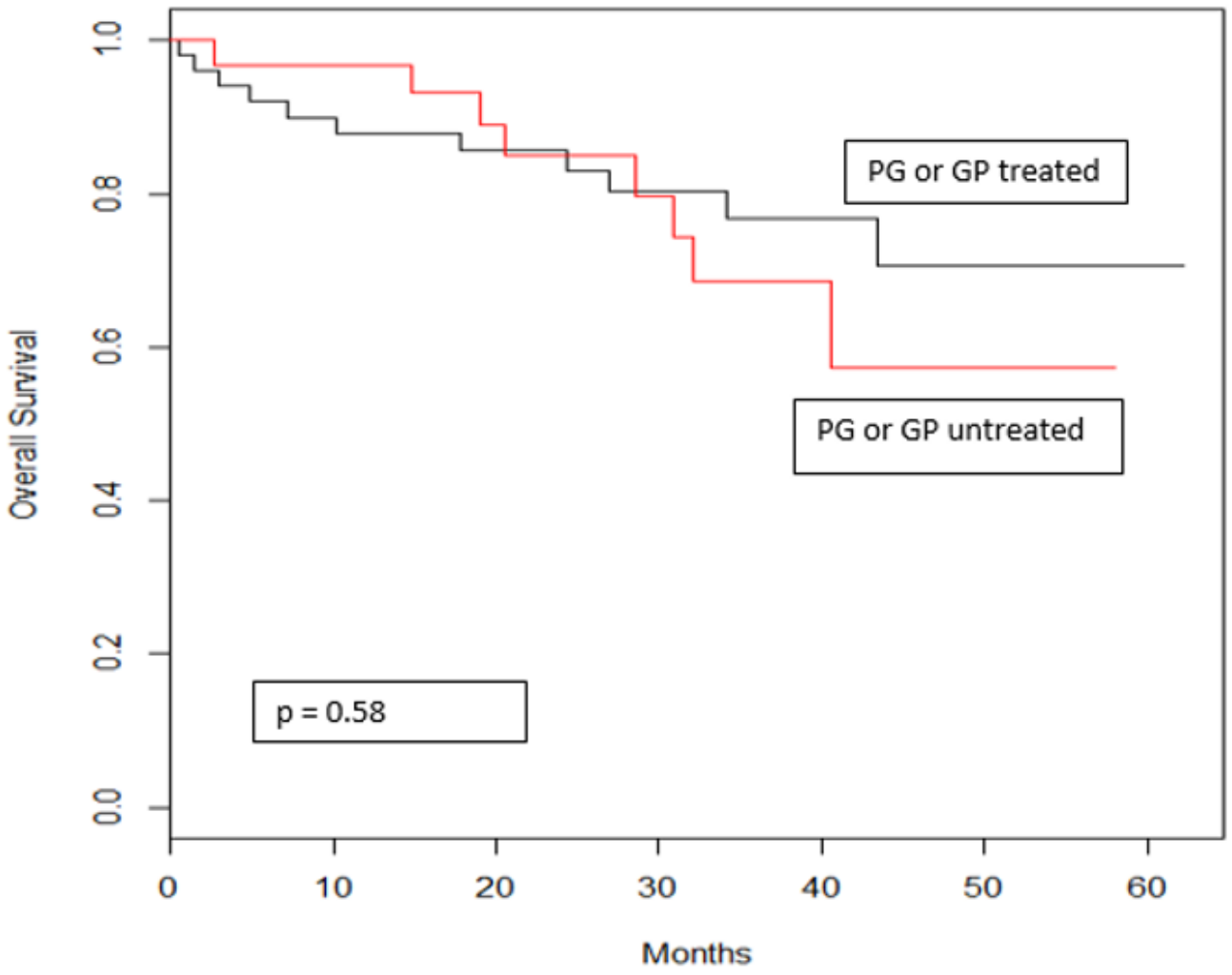

Figure 2

Kaplan-Meier Curve of Overall Survival