SINGLE CENTER PHARMACOECONOMIC ANALYSIS OF PALIFERMIN IN AUTOLOGOUS STEM CELL TRANSPLANTATION

BY

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Degree to be awarded: M.P.H.
Career MPH

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Heather Renfroe Johnson
M.P.H., Emory University, 2013
B.A., Emory University, 2008

Thesis Committee Chair: Edmund K. Waller, MD, PhD

An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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2013

Abstract

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BACKGROUND: Randomized clinical trials have shown palifermin reduces the incidence and severity of oral mucositis and its subsequent outcomes in patients with hematological malignancies receiving TBI-based conditioning regimens and autologous hematopoietic stem cell transplantation (HSCT). However, similar outcomes data for patients receiving non-TBI based conditioning is inconclusive. Our objective was to determine whether clinical and health care resource outcomes were different between patients who received palifermin and those who did not in the setting of HSCT following non-TBI based conditioning. METHODS: Patient data was retrospectively obtained on 524 consecutive patients with multiple myeloma (MM) or lymphoma who received autologous HSCT with melphalan 200 mg/m² or high-dose busulfan, cyclophosphamide, and etoposide conditioning between January 2002 and December 2010. Patients were stratified by diagnosis and multivariate analysis using generalized linear models was conducted for each outcome to compare treatment groups. Models were adjusted for differences in baseline characteristics. RESULTS: The analyses included 254 MM patients (162 palifermin, 92 control) and 270 lymphoma patients (167 palifermin, 103 control). PCA incidence was significantly lower in the palifermin-treated groups (MM: 13% vs. 53%, P<0.001; lymphoma: 46% vs. 68%, P<0.001). Similarly, the median duration of PCA use was significantly shorter among the palifermin group compared to the control group (MM: 0 days vs. 3 days, lymphoma: 0 days vs. 5 days). Palifermin treatment was not associated with a difference in overall survival (OS), days to neutrophil engraftment, or length of stay (LOS). The mean total transplant charges were significantly higher in the palifermin-treated group, after controlling for inflation (MM: $175K vs. $158K, P<0.001; lymphoma: $188K vs. $159K, P<0.001). CONCLUSION: In patients receiving non-TBI based conditioning regimens and autologous HSCT, palifermin significantly decreases PCA use, but significantly increases total charges associated with autologous HSCT. Palifermin administration was associated with an additional cost (as charges) of $11K (MM) and $15K (lymphoma) per day of PCA use (severe pain) avoided. Future research is suggested to evaluate the cost-effectiveness of palifermin use compared with other symptomatic treatments that reduce suffering without a direct effect on survival using validated measures for quality of life and pain symptoms.

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INTRODUCTION

Oral mucositis remains one of the most significant complications of high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT). Mucositis results from damage to epithelial lining of the oral cavity and ranges from mild erythema to severe ulceration. Clinical consequences of oral mucositis include pain, dehydration, malnutrition, and infection.[1] These consequences can lead to increased health care utilization such as increased use of opiod analgesics, increased total parenteral nutrition, and prolonged hospitalization.[2,3]

There is no standard therapy for oral mucositis in patients undergoing HSCT. Some recent studies have shown results supporting palifermin reduces oral mucositis in patients undergoing HSCT using low-level infrared laser therapy or cryotherapy.[4,5] However, palifermin, a recombinant human keratinocyte growth factor, is the only FDA-approved drug to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy and HSCT.

The initial label indication of palifermin approved by the FDA in 2004 was broad and included autologous and allogeneic transplant recipients. Among recipients of allogeneic HSCT from equally matched related and unrelated donors, results of a randomized, double-blind, placebo-controlled clinical trial indicated that palifermin treatment on three consecutive days before myeloablative conditioning and a single dose after conditioning did not reduce acute graft-versus-host-disease or the incidence of grade 3-4 oral mucositis.[6]

In autologous transplant recipients, the pivotal phase III trial that the FDA based approval upon, showed that the administration of palifermin for 3 days pre- and post- TBI-based myeloablative conditioning was associated with significant reductions in the incidence of WHO grade 3/4 oral mucositis, patient-reported throat and mouth soreness, the use of opiod analgesics, and the use of total parenteral nutrition (TPN).[7] A sub-set analysis of data from the registration trial suggested that the acquisition cost of palifermin is offset by decreased health care resource utilization.[8] Another study using the population from the registration trial

concluded a potential cost benefit of palifermin based upon reduced hospital duration, analgesic use, and parenteral nutrition.[9]

However, the study results of palifermin use in non-TBI based conditioning regimens and autologous HSCT are unclear. In 2011, the FDA amended the label indication of palifermin to exclude use with melphalan 200 mg/m² as a conditioning regimen. The basis for this recommendation was an EBMT trial in which the incidence of oral mucositis WHO grade 3/4 in patients who received high-dose melphalan was not significantly different between the groups that received 3 doses (pre-transplant conditioning) or 6 doses (pre-/post-conditioning) on the palifermin arm and a placebo arm.[10] Yet another trial examining the incidence of oral mucositis after palifermin administration for 3 days prior to conditioning with melphalan 200 or 140 found that patients who received palifermin experienced significantly less days of hospitalization, less need for opiod analgesics, TPN, and blood transfusions.[11] More published data supporting the use of palifermin in non-TBI based conditioning regimens and autologous HSCT is needed.

Based upon the initial FDA label indication, palifermin administration in autologous transplant recipients became standard practice at our institution for patients undergoing non-TBI based myeloablative conditioning and autologous HSCT. Following the update of the FDA label, our aim was to gain additional data to support the use of palifermin in this patient population. We had two questions: 1. Is palifermin effective in reducing mucositis in the setting of autologous HSCT following non-TBI based conditioning? 2. If palifermin is effective, what is its effect on health care resource utilization? To answer these questions, we undertook a retrospective study of myeloma and lymphoma patients transplanted following non-TBI based conditioning before and after the clinical introduction of palifermin. We hypothesized that palifermin would be effective in reducing IV narcotic use with patient-controlled-analgesia (PCA) (as a surrogate for oral mucositis) in the setting of non-TBI based conditioning for patients undergoing autologous HSCT. We also explored the effect of palifermin on other clinical outcomes including, days to neutrophil engraftment and overall survival (OS), and health resource outcomes, length of stay (LOS) and charges incurred during specified time periods pre- & post- HSCT.

METHODS

Study Design

This is a single-center, retrospective, observational, controlled study of patients receiving high-dose chemotherapy and autologous HSCT, comparing palifermin-treated patients to untreated controls. The Emory institutional review board approved use of patient data for this analysis.

Patients

The patient population included 254 multiple myeloma (MM) and 270 lymphoma patients who underwent autologous HSCT at Emory University Hospital between January 2002 and December 2010, for a total of 524 patients. Inclusion criteria included standard eligibility for transplant, absence of a prior autologous or allogeneic transplant, and the application of a uniform conditioning regimen, either melphalan 200 mg/m² for myeloma patients or high-dose busulfan, cyclophosphamide, and etoposide for lymphoma patients. Patients could not have been enrolled on any clinical trial utilizing investigational drugs. Palifermin-treated patients were identified through an automated analysis of pharmacy records. According to standard institutional practice at Emory, palifermin is administered per the label indication for a total of 6 doses, 60 mcg/kg/day IV, for 3 consecutive days before conditioning and 3 doses post-HSCT. Those patients who received at least 3 out of the 6 planned doses of palifermin were included in the analyses. Non-palifermin treated, control subjects included those patients who were transplanted prior to FDA approval of palifermin and those who did not receive palifermin after FDA approval for various reasons including physician discretion or patient declination due to associated costs or logistics of palifermin administration.

Statistical Methods

MM and lymphoma patients were analyzed separately using SAS version 9.3. Baseline characteristics, including sex, age, ethnicity, and disease status at transplant, were compared between the palifermin and control groups. Differences were assessed using Fisher's exact test

or the Kruskal-Wallis test. Disease status at transplant was classified into 4 categories based on treatment response according to the definitions established by the American Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research.

The primary end point was duration of IV narcotic use with patient-controlled-analgesia (PCA). Because this was a retrospective study and oral mucositis was not captured and graded consistently, we could not use oral mucositis of WHO grade 3 or 4 as our primary endpoint. We used PCA use as a surrogate for severe oral mucositis. Days of PCA use was calculated based on the number of days IV narcotics with a PCA pump were utilized during the transplant hospitalization. The duration was considered to be zero days among patients who did not utilize IV narcotics with a PCA pump.

Other end points included clinical outcomes, days to neutrophil engraftment and overall survival (OS), and health resource outcomes, length of stay (LOS) and charges incurred during specified time periods pre- & post- HSCT. Days to neutrophil engraftment was defined as the number of days from date of transplant to date of absolute neutrophil count (ANC) recovery where ANC recovery is defined as ANC of $\geq 0.5 \times 10^9$/L for three consecutive laboratory values obtained on different days. OS was defined at the time from transplantation to the last follow-up or death irrespective of the cause of death. The Kaplan-Meier method was used to estimate the probabilities of OS. LOS was defined as the number of days of hospitalization for HSCT.

Charges were used as a surrogate for cost. Differences in the ratio of costs to charges among hospitals or among different diseases were not relevant since we were only interested in comparing costs between treatment groups at our center. Charges were defined as all charges generated for professional or technical items or services during a specified time period and were adjusted for inflation using a standard inflation rate determined for each disease group. 2010 was used as the base year. Charges were grouped into 4 time periods: 5 days prior to admission for transplant, capturing the charges for the three daily injections of palifermin administered before conditioning, which were typically given in the outpatient setting; admission date to 30 days post-transplant, encompassing generally all of the transplant-related

charges; 31 days post-transplant to 100 days post-transplant, capturing long-term follow-up charges; and total charges from 5 days prior to admission to 100 days post-transplant.

Multivariate analysis using generalized linear models was conducted for each outcome to compare treatment groups. Models were adjusted for differences in baseline characteristics.

RESULTS

Patient Characteristics

In the MM cohort, the median age at the time of HSCT was 59 years in palifermin-treated patients versus 57 years in control patients (p=0.06); which is not statistically different. The lymphoma cohort was younger compared to the myeloma cohort, but similar to the myeloma cohort there is no statistical difference in the age between the palifermin-treated patients and controls. Median age for the palifermin-treated group was 48 years vs. 47 years (p=0.22). Disease status at transplant among lymphoma patients was the only baseline characteristic that was significantly different between the palifermin and control groups with a greater proportion of patients with partial response or stable disease in the palifermin group and a greater proportion of patients with complete response in the control group (P=0.02). All other baseline characteristics were similar in the palifermin and control groups for both MM and lymphoma patients (Tables 1 & 2).

Outcomes

The incidence of PCA use was significantly lower among the palifermin group than among the control group for both MM and lymphoma patients (MM: 13% vs. 53%, P<0.001; lymphoma: 46% vs. 68%, P<0.001, respectively) (Tables 3 & 4). Similarly, the median duration of PCA use was significantly shorter among the palifermin group than the control group (MM: 3 days vs. 0 days, lymphoma: 5 days vs. 0 days, respectively) (Tables 3 & 4). Of patients who utilized PCA, the number of days of PCA use was significantly higher in the control group. In the MM cohort, a significantly higher number of patients in the control group utilized PCA for 4 to 6, 7 to 9, and greater than 10 days compared to the palifermin-treated group (Figure 1A).

Similarly, in the lymphoma cohort, a significantly higher number of patients in the control group utilized PCA for 4 to 6 and greater than 10 days (Figure 1B). Three patients in the palifermin group and 7 patients in the control group were missing PCA data in the MM cohort and in the lymphoma cohort, 3 in the palifermin group and 9 in the control group were missing PCA data.

Mean duration to neutrophil engraftment was not different in the palifermin and control groups for either MM or lymphoma (Tables 3 & 4). For MM, the mean duration to neutrophil engraftment was 13.2 days in the palifermin group and 13.6 days in the control group (P=0.16) and the median was 13 days for both groups (Table 3). For lymphoma, the mean duration to neutrophil engraftment was 12 days in the palifermin group and 12.4 days in the control group (P=0.10) and the median was 12 days for both groups (Table 4). Similarly, OS was not different in the palifermin and control groups for either MM or lymphoma (Figure 2).

In MM patients there was no significant difference in length of stay (LOS) with a mean of 17.2 days in the palifermin group and 18 days in the control group (P=0.14) (Table 3). Also in lymphoma patients there was no significant difference in the mean LOS comparing the 167 patients who received palifermin to the group of 103 control patients who did not receive palifermin (22.5 days vs. 21.9 days, P=0.34) (Table 4).

MM patients who received palifermin had a higher mean charge for the five-day pre-transplant period compared with control patients ($13,590 vs. $6,410, P<0.001) (Table 3). The charges associated with the day of admission to day 30 post-transplant were similarly increased in the palifermin-treated group ($150,860 vs. $124,070, P<0.001) while day 31 to day 100 charges were lower in the palifermin-treated group compared to the control group ($10,600 vs. $27,170, P<0.001) (Table 3). In aggregate, mean charges for the palifermin-treated group were approximately $20,000 higher than the corresponding mean charges for the control group ($175,050 vs. $157,640, P<0.001) (Table 3).

Similar to the observation seen in the cohort of myeloma patients, in lymphoma patients palifermin administration increased charges in the five days preceding admission for high dose chemotherapy from $2,240 in the control group to $9,820 in the palifermin-treated

group (P<0.001) (Table 4). There was a difference of approximately $23,000 in the mean charges from day of admission to day 30 post-transplant from $135,950 in the control group to $160,720 in the palifermin treated group (P<0.001) (Table 4). There was a non-significant increase of long-term post-transplant charges from day 31 to day 100 in the control group compared with the palifermin-treated group ($20,640 vs. $17,520, P=0.135) (Table 4). Overall, similar to the observation in the cohort of MM patients, palifermin administration was associated with a significant increase of total charges associated with the transplant maneuver from $158,830 in the control group to $188,050 in the palifermin-treated group (P<0.001) (Table 4).

Figure 3 shows the distribution of charges adjusted to 2010 levels for the group of myeloma patients (Figure 3A) and the group of lymphoma patients (Figure 3B). Of note, the overall peak distribution of charges has shifted to the right associated with the administration of palifermin but the non-treated group includes a secondary tale of patients who had very high adjusted total charges that was not seen when palifermin was administered.

DISCUSSION

Oral mucositis is a frequent complication experienced by patients who undergo HSCT and may affect as many as 75% of all HSCT recipients.[12,13] In this patient population oral mucositis is typically associated with increased risks of serious infection and increased use of TPN, antibiotics, and pain medication.[3, 14] These complications can be costly. Palifermin has been shown to decrease the severity of oral mucositis and its subsequent outcomes in patients undergoing autologous HSCT following TBI-based conditioning regimens. Yet the published data surrounding the effects of palifermin in non-TBI-based conditioning regimens are inconsistent. This large retrospective analysis provides evidence on the impact of palifermin administration on clinical outcomes and healthcare resource utilization in the setting of autologous HSCT following non-TBI conditioning regimens.

The clinical impact of palifermin administration was a highly significant decrease in the incidence of parenteral narcotics administered through a PCA pump as well as a decrease in the

duration of PCA utilization in the palifermin-treated cohorts among both myeloma and lymphoma patients. The reduction in the incidence and duration of PCA use in the palifermin-treated group suggests that the palifermin-group experienced less pain, likely due to oral mucositis, than the control group. Results showed no significant impact of palifermin on overall survival, hematopoietic engraftment, or length of stay. The non-significant difference in overall survival between lymphoma patients in the palifermin-treated group and the control group (P=0.09) is likely due to the significant difference in disease status at the time of transplantation. These results support the administration of palifermin in the setting of autologous HSCT following non-TBI conditioning regimens.

Using charges generated over a wide range of years, adjusted to 2010 levels, we found that palifermin administration was associated with a significant increase of total charges both in the pre-admission phase of outpatient palifermin administration as well as during the transplant admission. These results conflict with the published data on health care utilization in the registration trial population. Studies using the patient population from the pivotal phase III trial that the FDA based approval upon suggested that the acquisition cost of palifermin is offset by decreased health care resource utilization.[8,9] Alternatively, our results prove that this was not the case. Palifermin administration was related to a significant increase in total charges related to transplantation independent of inflation of overall health care charges. Charges related to follow-up post-transplant (Day +31 to Day +100) were lower in the palifermin-treated groups. However, this is likely associated with a change in practice at our institution. During the time this population was transplanted we began discharging our patients back to their referring physician much earlier than we had been in the past. Because these charges are not reflected here and the time frame the palifermin group was transplanted was generally later than the controls, we would expected to see much lower charges from day 31 to day 100 in the palifermin group.

The results of this study are compelling evidence for decreased severe, symptomatic pain and significantly increased charges among palifermin-treated patients conditioned with non-TBI based conditioning regimens considering the uniform patient population and the large

sample size included in this study. However, there were limitations of this study, including the retrospective nature of analysis and the need to adjust charges for inflation to facilitate comparison of charges across a broad range of transplant dates. Additional limitations include the lack of formal scoring of mucositis. We used the incidence of parenteral narcotics administered through a PCA pump as a surrogate for severe oral mucositis. PCAs are commonly used for pain management associated with oral mucositis and represent our standard institutional practice for treating pain associated with severe oral mucositis post-HSCT. Thus, in spite of the lack of WHO mucositis scores, we believe that the use of PCA as a surrogate for severe mucositis supports the significant clinical affect of palifermin in the setting of non-TBI based conditioning.

In conclusion, palifermin is associated with a reduction in PCA use but an increase in overall charges related to transplantation. In an era of diminishing healthcare resources, it is certainly reasonable to question whether a 2 or 3 day reduction of PCA use is worth an additional $20,000 or more in overall charges. As palifermin administration was not associated with any impact on survival, a cost-effective analysis using quality-adjusted-life-years cannot be done based upon an effect on overall survival. However, palifermin administration was associated with an additional cost (as charges) of $11,000 (MM) and $15,000 (lymphoma) per day of PCA use (severe pain) avoided. The effect of palifermin administration thus equates to a relative cost of $3,000,000 to $5,000,000 for each year of life of severe pain (requiring parenteral narcotics delivered through a PCA) that is avoided. Future research is suggested to evaluate the cost-effectiveness of palifermin use compared with other symptomatic treatments that reduce suffering without a direct effect on survival using validated measures for quality of life and pain symptoms.

FINANCIAL DISCLOSURE STATEMENT

SOBI provided the funding for this study. SOBI representatives had no input into the data analysis or conclusions.

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TABLES

Table 1. Baseline Characteristics: Multiple Myeloma

Characteristic	Palifermin (N=162)	Control (N=92)	P value
Sex – no. (%)			
Female	80 (49)	35 (38)	0.09
Male	82 (51)	57 (62)	
Age – yr			
Median	59	57	0.06
Range	27-76	27-76	
Ethnicity – no. (%)			
Caucasian	90 (57)	61 (66)	0.14
Disease status at transplant – no. (%)			
≥ VGPR	17 (10)	10 (11)	0.97
Partial Response (1, 2, or 3+) or Stable	128 (79)	74 (80)	
Primary Refractory, Progressive, or Relapse	16 (10)	8 (9)	

Table 2. Baseline Characteristics: Lymphoma

Characteristic	Palifermin (N=167)	Control (N=103)	P value
Sex – no. (%)			
Female	60 (36)	43 (42)	0.37
Male	107 (64)	60 (58)	
Age – yr			
Median	48	47	0.22
Range	18-72	19-69	
Ethnicity – no. (%)			
Caucasian	113 (69)	76 (74)	0.41
Diagnosis – no.(%)			
HL	59 (35)	43 (42)	0.30
NHL	108 (65)	60 (58)	
Disease status at transplant – no. (%)			
Complete Response (1, 2, or 3+)	62 (37)	47 (46)	**0.02**
Partial Response (1, 2, or 3+) or Stable	83 (50)	34 (33)	
Primary Refractory, Progressive, or Relapse	22 (13)	22 (21)	

Table 3. Health Care Resource Utilization: MM

Variable	Palifermin (N=162)	Control (N=92)	P value
Incidence of PCA Use – no. (%)*	20 (13)	45 (53)	**<.001**
Duration of PCA Use – days*			
Mean	0.6	3.7	**<.001**
Median	0	3	
Neutrophil Engraftment – days			
Mean	13.2	13.6	0.16
Median	13	13	
LOS – days			
Mean	17.2	18.0	0.14
Median	17	18	
Charges – US $**			
5 Days Pre-Admission			
Mean	13,590	6,410	**<.001**
Median	12,800	1,010	
Admission date – Day +30			
Mean	150,860	124,070	**<.001**
Median	144,280	118,920	
Day+31 – Day+100			
Mean	10,600	27,170	**<.001**
Median	9,820	13,930	
Total Charges			
Mean	175,050	157,640	**<.001**
Median	167,820	143,200	

* 3 patients in the palifermin group and 7 patients in the control group were missing PCA data.
** Adjusted for inflation to 2010 charge rates.

Table 4. Health Care Resource Utilization: Lymphoma

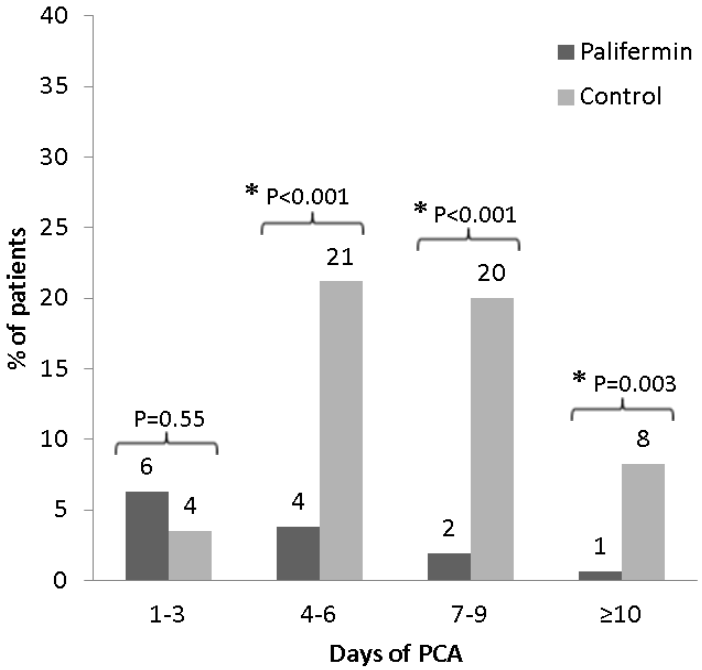
Variable	Palifermin (N=167)	Control (N=103)	P value
Incidence of PCA Use – no. (%)*	75 (46)	64 (68)	**<.001**
Duration of PCA Use – days*			
Mean	2.5	4.6	**0.002**
Median	0	5	
Neutrophil Engraftment – days			
Mean	12.0	12.4	0.10
Median	12	12	
LOS – days			
Mean	22.5	21.9	0.34
Median	22	22	
Charges – US $**			
5 Days Pre-Admission			
Mean	9,820	2,240	**<.001**
Median	8,160	0	
Admission date – Day +30			
Mean	160,720	135,950	**<.001**
Median	152,000	131,150	
Day+31 – Day+100			
Mean	17,520	20,640	0.135
Median	8,420	11,200	
Total Charges			
Mean	188,050	158,830	**<.001**
Median	168,570	148,590	

* 3 patients in the palifermin group and 9 patients in the control group were missing PCA data.
** Adjusted for inflation to 2010 charge rates.

FIGURES

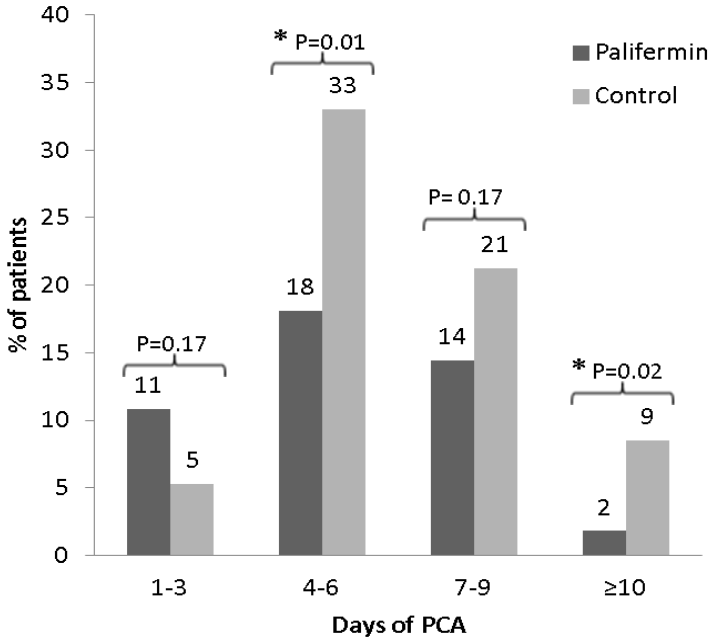
Figure 1. PCA Use

A. Multiple Myeloma



* Denotes a significant difference between the palifermin and control group using Fisher's exact test.

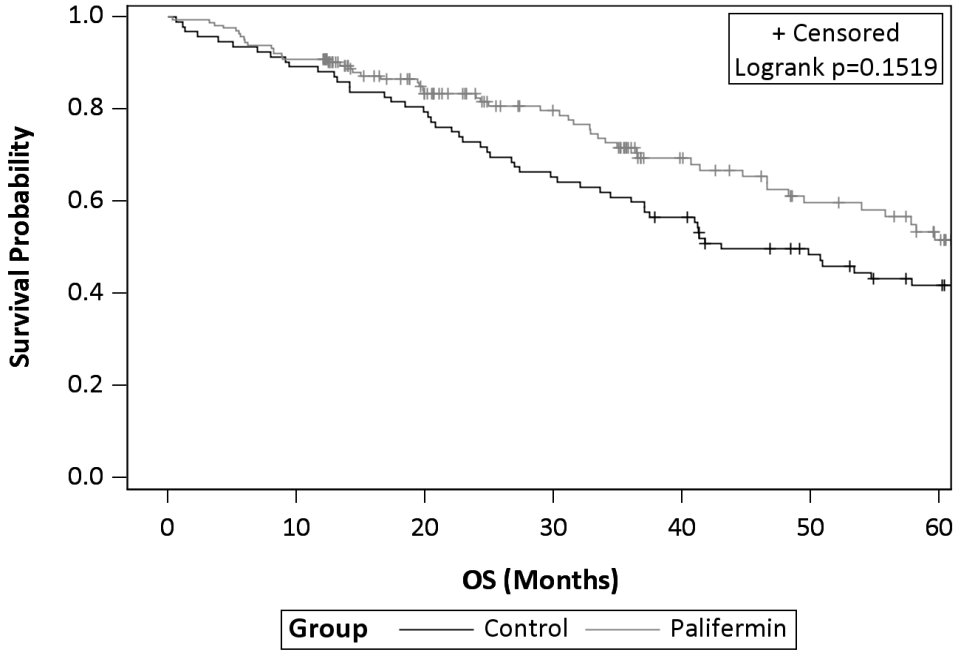
B. Lymphoma



* Denotes a significant difference between the palifermin and control group using Fisher's exact test.

Figure 2. Survival Curves

A. Multiple Myeloma



B. Lymphoma

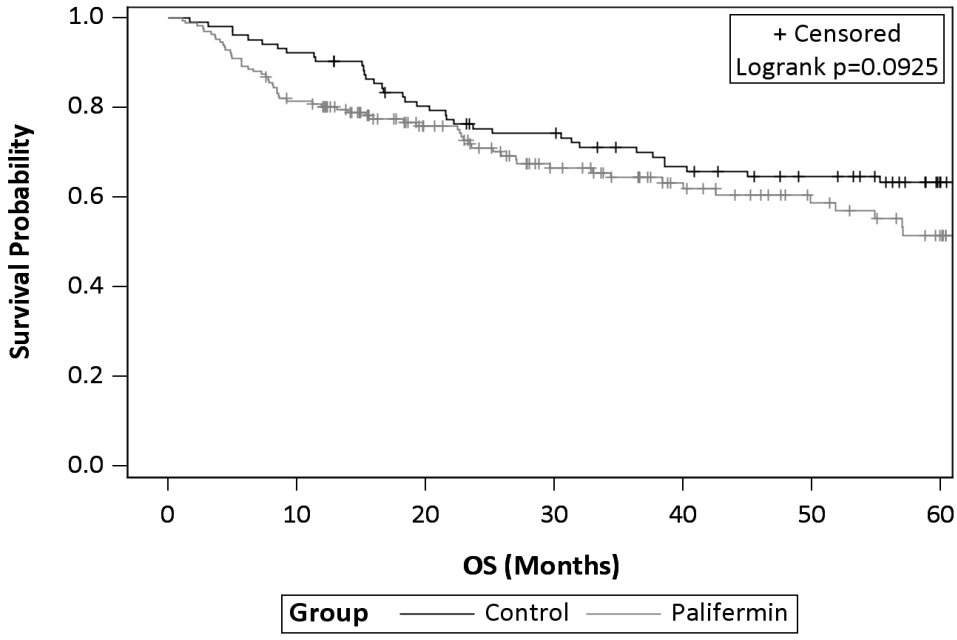
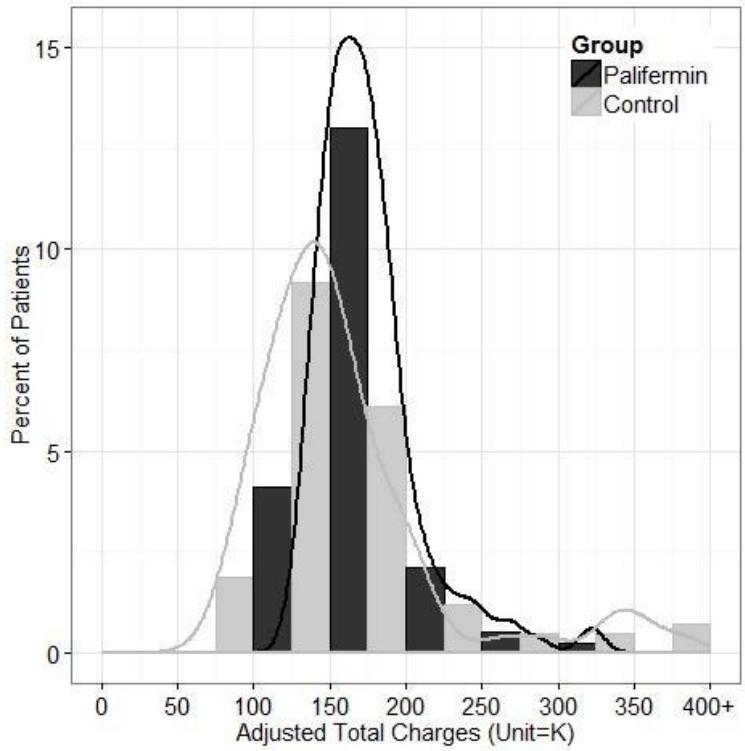


Figure 3. Distribution of Charges

A. Multiple Myeloma



B. Lymphoma