Pharmacoeconomic Analysis of Palifermin to Prevent Mucositis among Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

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Pharmacoeconomic analysis of palifermin to prevent mucositis among patients undergoing autologous hematopoietic stem cell transplantation

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Abstract

Prior trials have shown benefits of palifermin in reducing the incidence and severity of oral mucositis in patients with hematological malignancies undergoing autologous hematopoietic stem cell transplantation (HSCT) with total body irradiation (TBI)-based conditioning regimens. Similar outcomes data are lacking for patients receiving non-TBI-based regimens. We performed a retrospective evaluation on the pharmacoeconomic benefit of palifermin in the setting of non-TBI-based conditioning and autologous HSCT. 524 patients that underwent autologous HSCT for myeloma (melphalan 200 mg/m²) and lymphoma (high-dose busulfan, cyclophosphamide, and etoposide) as preparative regimen between January 2002 and December 2010 were analyzed. Usage of patient controlled analgesia (PCA) was significantly lower in the palifermin-treated groups (myeloma: 13% vs. 53%; p<0.001; lymphoma: 46% vs. 68%; p<0.001). Median total transplant charges were significantly higher in the palifermin-treated group, after controlling for inflation (myeloma: $167,820 vs. $143,200, p<0.001; lymphoma: $168,570 vs. $148,590, p<0.001). Palifermin treatment was associated with a difference in days to neutrophil engraftment, length of stay and overall survival; and was associated with an additional cost of $5.5K (myeloma) and $14K (lymphoma) per day of PCA avoided. Future studies are suggested to...
evaluate the cost-effectiveness of palifermin compared with other symptomatic treatments to reduce transplant toxicity using validated measures for pain and quality of life.

Keywords
palifermin; recombinant human keratinocyte growth factor; mucositis; pharmacoeconomic analysis

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 opioid analgesics, increased total parenteral nutrition (TPN), and prolonged hospitalization [2,3]. Currently, there is no standard therapy for decreasing the incidence or severity of oral mucositis in patients undergoing HSCT. Though, some recent studies have shown early promising results in reducing the incidence of oral mucositis in patients undergoing HSCT using low-level infrared laser therapy or cryotherapy[4,5]. Palifermin, a recombinant human keratinocyte growth factor, is the only Food and Drug Administration (FDA)-approved agent proven 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 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, administration of palifermin for 3 days pre- and post- TBI-based myeloablative conditioning was associated with significant reductions in the incidence of World Health Organization (WHO) grade 3-4 oral mucositis, patient-reported outcomes of throat and mouth soreness, use of opioid analgesics, and the use of TPN [7]. A sub-set analysis of data from the registration trial suggested that the acquisition cost of palifermin is compensated by decreased health care resource utilization [8]. Another published report from the registration trial also confirmed a potential cost-benefit advantage for the usage of palifermin based upon reduced hospital duration, analgesic use, and TPN utilization [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 its use for mucositis prevention with melphalan 200 mg/m² as a conditioning regimen. The basis for this recommendation was a trial from The European Group of Blood and Marrow Transplantation (EBMT)comparing 3 doses of palifermin (pre-transplant
conditioning) or 6 doses (pre/post conditioning) to a placebo arm where the incidence of WHO grade 3-4 mucositis was not significantly different between the two groups [10]. A subsequent trial using palifermin 3 days prior to conditioning with melphalan 200mg/m² or 140mg/m² reported palifermin-treated patients experienced significantly less days of hospitalization, less need for opioid analgesics, TPN, and blood transfusions [11]. The conflicting data raised the question of utility of palifermin in autologous HSCTs using non-TBI based conditioning regimens.

Based on the initial FDA label indication, palifermin administration in autologous transplant recipients became a 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: First, is palifermin effective in reducing mucositis in the setting of autologous HSCT following non-TBI based conditioning? Second, 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 parameters including, days to neutrophil engraftment, overall survival (OS), health care resource utilization, length of stay (LOS) and charges incurred during specified time periods pre- & post- HSCT.

METHODS

Study Design

This is a single-center, retrospective study comparing palifermin-treated patients to untreated controls for pre-specified end points among patients receiving high-dose chemotherapy and autologous HSCT. Institutional review board approval was obtained to use patient data for this analysis.

Patients

The patient population included 254 myeloma and 270 lymphoma patients who underwent autologous HSCT at our institution between January 2002 and December 2010, for a total of 524 patients. In the treatment group, consecutive patients that were treated with palifermin from 05/2005 until 12/2010 were included in the analysis. In the control group, we included 164 patients treated before FDA approval of palifermin (01/2002-04/2005) and 31 patients transplanted after the FDA-approval of palifermin who did not receive palifermin following FDA approval for various reasons including physician discretion or patient declination due to associated costs or logistics of palifermin administration. To make the data less ambiguous and minimize bias, inclusion criteria were restricted to patients receiving uniform conditioning regimen of melphalan 200 mg/m² for myeloma patients and high-dose busulfan, cyclophosphamide, and etoposide (Bu/Cy/VP-16) for lymphoma patients. Patients who had received a prior autologous or allogeneic transplant or enrollment on any clinical
trial utilizing investigational drugs were excluded from analysis. Palifermin-treated patients were identified through an automated analysis of pharmacy records. According to standard institutional practice at our institution, palifermin is administered per the label indication for a total of 6 doses, 60 mcg/kg/day intravenously (IV), for 3 consecutive days before receiving conditioning regimen 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 in the palifermin-treated group.

**Statistical Methods**

Myeloma and lymphoma patients were analyzed separately using SAS version 9.3. Baseline characteristics, including sex, age, ethnicity, and disease status at transplant as well as primary diagnosis for the lymphoma patients 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 3 categories based on treatment response according to the definitions established by the American Society for Blood and Marrow Transplantation (ASBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR). Due to the nature of our study and the inherent limitations associated with a retrospective analysis, the primary end point used in this analysis was duration of IV narcotic use with PCA as a surrogate for severe oral mucositis. Due to inconsistencies in the grading of oral mucositis, we could not use WHO grade 3 or 4 oral mucositis as our primary endpoint. 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 OS; and health care resource utilization, 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 and the log-rank test was used to test for differences between groups. 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. Inflation factors for the actual charges for myeloma and lymphoma patients were calculated separately, as the rate of increase in charges varied according to adoption of disease-specific supportive care protocols (Supplementary Figure 1). The calculated inflation factors for myeloma and lymphoma patients were 1.07 and 1.04 respectively. 2010 was used as the base year. Charges were grouped into 3 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 were summarized as total charges from 5 days prior to admission to 100 days post-transplant. Multivariable analysis using generalized linear models was conducted for each outcome to compare treatment groups. Cox proportional hazards regression was used for OS; ANCOVA for days to neutrophil engraftment and LOS; logistic regression for incidence of PCA use; and negative binomial regression for duration of PCA use and charges due to their skewed distributions. Models were adjusted for differences in baseline characteristics.

RESULTS

The median age of myeloma patients at the time of HSCT was 59 years in palifermin group vs. 57 years in control group. The lymphoma cohort was younger compared to the myeloma cohort, and there were no significant differences in age between the palifermin group vs. controls is not significantly different (48 years vs. 47 years; p=0.22). All the baseline characteristics were similar in the palifermin and control groups for both myeloma and lymphoma patients, except for disease status in the lymphoma patients (Table 1).

The incidence of PCA use was significantly lower among the palifermin group than among the control group for both myeloma and lymphoma patients (myeloma: 13% vs. 53%, p<0.001; lymphoma: 46% vs. 68%, p<0.001, respectively) (Table 2). Similarly, the median duration of PCA use was shorter among the palifermin group (myeloma: 0 days vs. 3 days, p<0.001; lymphoma: 0 days vs. 5 days; p=0.002, respectively) (Table 2). The median time to neutrophil engraftment and LOS was not different comparing the palifermin to the control groups for both myeloma and lymphoma patients (Table 2).

As expected, both myeloma and lymphoma patients who received palifermin had a higher median charge during the five-day pre-transplant period (myeloma: $12,800 vs. $1,010, p<0.001; lymphoma: 8,160 vs. 0; p<0.001) (Table 2). Similar trends were seen with charges associated from the day of admission to day 30 post-transplant (myeloma: $144,280 vs. $118,920, p<0.001; lymphoma: $152,000 vs. $131,150, p<0.001). Interestingly, median charges from day 31 to day 100 were lower in the palifermin-treated group in both myeloma and lymphoma patients compared to the control group (myeloma: $9,820 vs. $13,930, p<0.001; lymphoma: $8,420 vs. $11,200, p<0.001) even though in aggregate, median charges for the palifermin-treated group were higher than the corresponding median charges for the control group (myeloma: $167,820 vs. $143,200, p<0.001; lymphoma: $168,570 vs. $148,590, p<0.001) (Table 2). Figure 1 illustrates the distribution of charges adjusted to 2010 levels for myeloma patients (Figure 1A) and lymphoma patients (Figure 1B). Of note, the overall peak of the distribution of charges has shifted to the right for the palifermin treated patients in comparison to the control group, but the control group includes a secondary tail of patients who had very high adjusted total charges that was not seen in palifermin treated patients. The OS was not different in the palifermin-treated and control groups for both myeloma (Figure 2A) and lymphoma (Figure 2B) patients. Figures 3 and 4 illustrate the breakdown of itemized charges according to categories for myeloma and lymphoma, respectively. Of note, the fraction of charges related to pharmacy was larger in
the palifermin-treated group of myeloma patients (43% of charges) compared with the non-
apifermin-treated myeloma patients (32% of charges), while there was not a corresponding
increase in pharmacy charges comparing palifermin-treated versus control lymphoma
patients. The larger increase in pharmacy charges seen in the palifermin-treated myeloma
patients reflects other changes in supportive care among more recently transplanted
myeloma patients, including the protocol-specified use of post-transplant G-CSF, a practice
change that did not occur in lymphoma patients undergoing auto-transplant.

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. Our large retrospective analysis provides insight on
the impact of palifermin administration on clinical outcomes and healthcare resource
utilization in the setting of autologous HSCT following non-TBI conditioning regimens.

Clinically, palifermin administration in patients undergoing HSCT resulted in a significant
decrease in the incidence of parenteral narcotics administered through PCA and also
decreased 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 these patients experienced less pain, likely due to
oral mucositis, than the control group. Other hematopoietic engraftment parameters of
neutrophil engraftment and length of stay are similar in both cohorts for both disease groups.
These results support the administration of palifermin for decreasing severity of mucositis in
the setting of autologous HSCT following non-TBI conditioning regimens.

From the economic perspective, 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 hospitalization for transplant admission. These higher
charges are likely related to the acquisition costs of palifermin and the associated
administration costs. The results conflict with the published data on health care utilization in
the registration trial population. Studies using the patient population from the phase III trial,
on which the FDA based approval for palifermin for this particular indication was based on,
suggested that the acquisition cost of palifermin is offset by decreased health care resource
utilization [8,9]. Analysis of a large number of patients in our institutional database indicates
that this was not the case. Palifermin administration was associated with 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. This may reflect the less long term sequelae of oral mucositis in the control group or changes in practice in more recent years associated with earlier transfer of patients out of the health care system (where charges were captured) back to their local referring oncologist (where charges were not captured). However the equivalent overall survival between the palifermin and control groups suggest no significant impact of severity of mucositis on survival.

Strengths of our study include the sample size and uniformly treated myeloma and lymphoma patient populations. However, certain limitations 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 limit the impact of our findings in recommendation to change practice. Additional limitations include the lack of uniform clinical scoring of mucositis that was compensated by the use of PCA as a surrogate end point of incidence of 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. 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 effect of palifermin in the setting of non-TBI based conditioning.

In conclusion, palifermin is associated with a reduction in PCA use and an associated reduction in severe mucositis. However, there is a cost for prevention of pain and suffering associated with severe mucositis. To provide a perspective for future research in this area, we have estimated the costs associated with each day of severe pain avoided by using days of PCA use avoided as an estimator of severe pain. Adjusting for inflation to 2010 rates, the average cost of palifermin administration was $17,409 (myeloma) and $29,221 (lymphoma), which translates to an additional cost of $5,511 (myeloma) and $13,792 (lymphoma) per day of PCA use (severe pain) avoided. From a patient perspective, reduction in a day of severe mucositis that requires treatment with parenteral narcotics with a PCA may be worth the additional daily charges. Further research is suggested to evaluate the cost-effectiveness of palifermin use compared with other symptomatic treatments that reduce transplant toxicities using validated measures for pain and quality of life.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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REFERENCES


Figure 1.
Distribution of Charges
Figure 2.
Overall Survival
Figure 3.
Pie Charts of Adjusted Charges 5 Days Pre-Admit to 30 Days Post-Admit for Myeloma
Figure 4.
Pie Charts of Adjusted Charges 5 Days Pre-Admit to 30 Days Post-Admit for Lymphoma
### Table 1

**Baseline Characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Myeloma</th>
<th></th>
<th>P value</th>
<th>Lymphoma</th>
<th></th>
<th>P value</th>
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<td></td>
<td>Palifermin (N=162)</td>
<td>Control (N=92)</td>
<td></td>
<td>Palifermin (N=167)</td>
<td>Control (N=103)</td>
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<tr>
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</tr>
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<td>Female</td>
<td>80 (49)</td>
<td>35 (38)</td>
<td>0.09</td>
<td>60 (36)</td>
<td>43 (42)</td>
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<td>107 (64)</td>
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<td></td>
<td></td>
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<td></td>
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<td>57</td>
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<td>47</td>
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<tr>
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<td>18-72</td>
<td>19-69</td>
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<tr>
<td>Ethnicity – no. (%)</td>
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<td>Caucasian</td>
<td>90 (57)</td>
<td>61 (66)</td>
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<td>113 (69)</td>
<td>76 (74)</td>
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<td>Disease status at transplant – no. (%)</td>
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<td>≥ VGPR</td>
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<td>62 (37)</td>
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<td>128 (79)</td>
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<td>83 (50)</td>
<td>34 (33)</td>
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<tr>
<td>Primary Refractory, Progressive, or Relapse</td>
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<td>8 (9)</td>
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<td>22 (13)</td>
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<td>Diagnosis – no. (%)</td>
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<tr>
<td>HL</td>
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<td>59 (35)</td>
<td>43 (42)</td>
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<td>_</td>
<td>108 (65)</td>
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Table 2

Health Care Resource Utilization

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<th>Variable</th>
<th>Myeloma</th>
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<th>P value</th>
<th>Lymphoma</th>
<th>Palifermin (N=167)</th>
<th>Control (N=103)</th>
<th>P value</th>
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<tr>
<td>Incidence of PCA Use – no. (%)</td>
<td>20 (13)</td>
<td>45 (53)</td>
<td>&lt;.001</td>
<td>75 (46)</td>
<td>64 (68)</td>
<td>&lt;.001</td>
<td></td>
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<tr>
<td>Duration of PCA Use – days</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>0.6</td>
<td>3.7</td>
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<td>2.5</td>
<td>4.6</td>
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<td>Neutrophil engraftment – days</td>
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<td>13.2</td>
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<td>12</td>
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<td>LOS – days</td>
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<tr>
<td>Mean</td>
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<td>&lt;.001</td>
<td>9,820</td>
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<tr>
<td>Mean</td>
<td>150,860</td>
<td>124,070</td>
<td>&lt;.001</td>
<td>160,720</td>
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<tr>
<td>Median</td>
<td>144,280</td>
<td>118,920</td>
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<td>131,150</td>
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<td>Day+31 – Day+100</td>
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<tr>
<td>Mean</td>
<td>10,600</td>
<td>27,170</td>
<td>&lt;.001</td>
<td>17,520</td>
<td>20,640</td>
<td>0.135</td>
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<tr>
<td>Median</td>
<td>9,820</td>
<td>13,930</td>
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<td>8,420</td>
<td>11,200</td>
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<td>Total Charges</td>
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<tr>
<td>Mean</td>
<td>175,050</td>
<td>157,640</td>
<td>&lt;.001</td>
<td>188,050</td>
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<tr>
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<td>143,200</td>
<td></td>
<td>168,570</td>
<td>148,590</td>
<td></td>
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</tr>
</tbody>
</table>

* Missing PCA data (myeloma: 3 patients in palifermin group and 7 in control group; lymphoma: 3 patients in palifermin group and 9 in control group).

** Adjusted for inflation to 2010 charge rates.