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Melphalan 180 mg/m2 Can Be Safely Administered As Conditioning Regimen before an Autologous Stem Cell Transplantation (ASCT) in Multiple Myeloma Patients with Creatinine Clearance 60 mL/min/1.73 m2 or Lower with Use of Palifermin for Cytoprotection: Results of a Phase I Trial

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Abstract

High-dose melphalan 140 mg/m^2 is the standard of care for patients with multiple myeloma (MM) with renal insufficiency (RI). Palifermin as a cytoprotective agent has demonstrated efficacy in reducing the intensity and duration of oral mucositis (OM) in patients who receive intensive chemotherapy/radiotherapy. There is no prospective data on the use of palifermin in patients with MM with RI. Eligibility criteria: creatinine clearance ≤60 mL/minute/1.73 m^2, age >18 years, no dialysis, no active OM, and a suitable candidate for autologous stem cell transplant (ASCT). Melphalan dose ranged from 140 to 200 mg/m^2 and escalated at the increment of 20 mg/m^2. Six dosages of palifermin 60 mcg/kg/day were given intravenously between day −5 to day +3. Dose escalations were to stop if dose-limiting toxicities (DLTs) occurred at melphalan dose in ≥2 of 3 patients, with that dose declared as the maximal administered dose and the level below where ≤1 of 6 patients had DLTs was considered the maximally tolerated dose (MTD). Nineteen patients were enrolled from June 2007 to June 2011. Data on 15 evaluable patients is reported as 4 patients were removed. Median age was 59 years (range, 36–67 years). The overall incidence of OM ≥ grade 3 was 53% (8 of 15) and a median duration of ≥ grade 3 OM was 6.5 days (range, 3–42 days). One patient in L2 (melphalan 160 mg/m^2) developed atrial fibrillation on day +9. Two patients in L4 (melphalan 200 mg/m^2) developed grade 4 OM, hence reaching DLT. No DLT was observed in 6 patients enrolled in L3 (melphalan 180 mg/m^2). Palifermin has permitted safe dose escalation of melphalan up to 180 mg/m^2 in patients with RI.

Keywords

Myeloma; Palifermin; High-dose melphalan; Autologous stem cell transplant

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INTRODUCTION

Renal failure is present in 20% to 50% patients with multiple myeloma (MM) and plays a significant role in therapeutic decision-making process [1–5]. Although autologous stem cell transplant (ASCT) with high-dose melphalan conditioning is considered the standard of care for myeloma [6–11], patients with renal insufficiency (RI) are often excluded from studies involving ASCT due to increased treatment-related morbidity and mortality. However, multiple studies have shown that RI should not be an exclusion criterion and early ASCT could be helpful in treating patients with MM with RI [2–5]. Melphalan 200 mg/m^2 is the recommended dose of conditioning regimen for patients with normal renal function [11,12]. Due to increased morbidity and mortality observed with melphalan 200 mg/m^2 in patients with RI, it is recommended that the dose of melphalan should be reduced to 140 mg/m^2 [5,13]. It is evident that renal failure is associated with increased toxicity of melphalan [2,3,5,13]. Badros et al. [13] showed that melphalan 200 mg/m^2 without a cytoprotective agent is associated with a higher incidence of oral mucositis (OM; 93%) along with other drug-related toxicities. This led them to decrease the melphalan dose to 140 mg/m^2 in patients with serum creatinine >2 mg/dL. Despite reduced melphalan dose and patients receiving standard supportive care only, the incidence of OM was 67%. Therefore, OM prevention is a pre-requisite for dose intensification of melphalan in patients with RI.

Unfortunately, there is a considerable dearth of literature prospectively addressing this issue due to lack of suitable supportive care options. Currently, palliation and treatment of OM is achieved through topical and systemic analgesia [14]. Novel agents such as velafermin (no longer available) and amifostine have been evaluated with mixed results [15–17]. They have not been shown to improve outcomes, and thus there are no consensus recommendations for their use.

Palifermin (Kepivance) is a recombinant human keratinocyte growth factor, which is approved for decreasing the incidence and duration of severe OM in patients with hematological malignancies undergoing chemo/radiotherapy followed by stem cell rescue [18–23]. Spielberger et al. [21] reported that severe OM was reduced to 63% in the palifermin group compared with 98% in the placebo group. These measures can add considerable expense to the cost of ASCT. However, this disbursement can be justified if these cytoprotective agents prevent melphalan dose reduction in patients with myeloma with RI and result in improvement of response, OM, toxicity profile, and quality of life.

This phase I dose escalation trial was designed to find the maximal tolerated dose (MTD) of melphalan combined with palifermin in patients with RI who were undergoing ASCT for MM. To the best of our knowledge, there are no studies that have specifically addressed the role of any cytoprotective agent in patients with MM with RI undergoing ASCT.

MATERIALS AND METHODS

This phase I trial was registered in the clinical-trials. gov database (NCT00482846). The study was conducted at Karmanos Cancer Institute, Detroit, Michigan, and was approved by the Wayne State University Institutional Review Board. It was conducted in accordance with the Declaration of Helsinki.

Eligibility

Patients were eligible for the study if they qualified for ASCT per institutional criteria and had at least 2.0 × 10^6 CD34+ cells/kg cryopreserved for ASCT. They also had to have an Eastern Cooperative Oncology Group performance status of ≤2, stage 2 to 3 MM, age ≥18 years, creatinine clearance ≤60 mL/minute/1.73 m^2, total bilirubin <1.5 × institutional upper

limit of normal, and an aspartate aminotransferase/alanine aminotransferase <3 × institutional upper limit of normal. Patients with baseline oral lesions, a history of allergic reactions to melphalan, dependence on dialysis, and prior exposure to palifermin were deemed ineligible.

Dose Calculations

The melphalan dose was calculated using actual body weight (ABW) except when the ABW was >40% above the ideal body weight (IBW), and then adjusted body weight (AdBW) was used. Men: IBW (kg) = 50 + 0.91 × (height in cm 152); women: IBW (kg) = 45 + 0.91 × (height in cm 152) and AdBW (kg) = IBW + 0.25 × (actual weight − IBW).

Palifermin was administered on days −5, −4, and −3 and then repeated on day +1, +2, and +3 (peripheral blood stem cells infused on day 0). Palifermin dose was 60 mcg/kg/day of ABW unless ABW was >40% above the IBW, and then AdBW was used for dose. There was a 24-hour interval between palifermin and melphalan administration. Participants received palifermin as once daily intravenous bolus. No study drug dose adjustments were allowed. Filgrastim 5 mcg/kg/day was administered subcutaneously, starting on day +6, and continued until the absolute neutrophil count was >1500/mm^3 for 3 consecutive days.

In order to minimize the effect of confounding variables, use of agents such as amifostine, oral cryotherapy during chemotherapy administration, “magic mouthwash” or “miracle mouthwash” solutions containing chlorhexidine or hydrogen-peroxide or benadryl, IL-11(Neumega), granulocyte macrophage-colony stimulating factor, sucralfate in suspension form, povidone-iodine rinses, glutamine as a prophylactic agent for OM, and other investigational agents, were not allowed during the study. Use of sucralfate tablets was not prescribed.

Study Design

Dose level 1 began with melphalan at 140 mg/m^2 with palifermin. If there no grade 3 dose-limiting toxicity (DLT) events were noted by day 30 after ASCT, an additional cohort of 3 patients was entered at the next dose level. Subsequent dose escalations were planned at 20 mg/m^2 increments in cohorts of 3 patients. Dose escalations were to stop if 2 or more DLT events occurred at melphalan dose, with that dose declared as the maximal administered dose. If a single DLT was noted in a cohort of 3 patients, 3 additional patients were entered at that dose, and dose escalation proceeded only if no additional DLTs (ie, 1 of 6) were noted. If 1 or more of these 3 additional patients suffered DLTs, then dose escalations were to stop, and this dose was declared the maximally administered dose. MTD was the highest dose level below the maximally administered dose in which ≤1 DLTs were observed in 6 patients at that level. If a full cohort of 3 patients were entered at a given level without the observation of grade ≥3 palifermin-related toxicity, but follow-up of day +30 was not achieved in all 3 patients, dose escalation was still permitted to the next level. A patient not receiving all 6 doses of palifermin was replaced in the same dose level. Swedish Orphan Biovitrum pharmaceuticals provided palifermin as an investigational agent for this clinical trial. Palifermin is commercially available, and the approximate cost of a 5-mg vial is US $4700.

Dose-Limiting Toxicities

Grade ≥3 hematological toxicity was considered acceptable for this study. Grade 4 oral mucositis, grade 4 diarrhea, ≥ grade 3 skin rash, grade 4 elevations of amylase and lipase (symptomatic), and ≥ grade 3 cardiac toxicity were considered as DLTs. Any other grade 3 toxicity that is determined by the principal investigator to be probably or definitely related to study drugs will be considered as a DLT.

Patient Monitoring and Follow-Up

Patients who received all 6 doses of palifermin were followed until day +100 as part of the protocol and underwent workup to determine the response to treatment on day +28 and day 100 (+/−7 days). Starting on day −2, or with the administration of high-dose melphalan, oral cavity assessments were performed daily using the World Health Organization (WHO) oral toxicity scale and continued until OM resolved completely (WHO = 0) or until day +28 (Table 1). The bone marrow transplant attending physician scheduled for inpatient rounding performed daily OM assessments during the inpatient stay. If the patient was discharged from the hospital without complete resolution of OM, they were followed twice weekly in the outpatient clinic until complete resolution. The bone marrow transplant attending physician in the outpatient clinic performed this assessment. Our primary objective was to determine the MTD of melphalan in patients with RI who underwent ASCT for myeloma when treated with palifermin to prevent OM. The evaluation of the efficacy of this regimen, regimen-related toxicities, and the overall response to therapy at day +100 constituted the secondary objectives.

RESULTS

Between June 2007 and June 2011, 19 patients were enrolled in the trial. Four patients did not receive full doses of palifermin and were rendered nonevaluable. The median age was 59 years (range, 36–67 years). Eight patients were men. The median creatinine clearance was 42.8 mL/minute (range, 29–60 minute).

Median baseline creatinine was 1.4 mg/dL (0.7–2.3). All patients had Karnofsky score ≥70%. Thirteen patients (87%) had stage 3 chronic kidney disease (CKD), 1 patient had stage 4 CKD, and 1 patient had stage 2 CKD. No patient had stage 5 CKD.

Four patients at the time of ASCT were in complete response (CR), 3 patients had very good partial response (VGPR), 5 had progressive disease (PD), and 3 had partial response (PR). Light chain disease was seen in 4 patients. IgG isotype was present in 8 patients. Two patients had received prior ASCTs. Ten patients received 2 prior regimens for treatment before the ASCT (Table 2).

Median number of CD34 cells collected was 5.74×10^6 cells/kg (range, 4.7–13.15). Median number of CD34 cells infused was 4.15×10^6 cells/kg (range, 2.58–8.03). Median number of days for neutrophil engraftment was 12 (range, 11–21 days). Median number of days to platelet engraftments was 19 (range, 0–86 days). Median number of days in the hospital was 16 (range, 12–74 days). Median duration of follow-up for surviving patients was 16.5 months (range, 3–44 months).

Melphalan was given in doses up to and including 200 mg/m^2 (n = 3) at level 4. Three patients were enrolled in dose level 1 (melphalan 140 mg/m^2). No DLTs were observed in level 1, so 3 patients were added to level 2 (melphalan 160 mg/m^2). Subsequently, 3 patients were added to level 3 (melphalan 180 mg/m^2) when no DLTs were seen in level 2. Similarly, 3 patients were added to level 4 (melphalan 200 mg/m^2), and 1 death occurred in level 4 due to multiorgan failure as the result of multiple grade 4 toxicities and grade 3 infections.

Another patient in level 4 developed grade 3 DLTs (congestive heart failure, interstitial pneumonitis, and bullous dermatitis). Dose escalation was stopped as 2 DLT events occurred in level 4. The next cohort of patients was added in level 3 (180 mg/m^2). No DLTs were seen in this group, hence reaching MTD.

The overall incidence of OM ≥ grade 3 was 53% (8 of 15), with median time to resolution of severe OM was 6.5 days (range, 3–42 days). Patients who did not develop any severe OM were not included in the calculation of median and range. In level 3, 1 patient had no OM, 4 of 6 patients developed grade 3 OM and no grade 4 OM was observed. One patient in level 3 had unresolved grade 2 OM on day 28, which improved to grade 1 on day 35. Resolution of OM was not documented until day 96 because the patient did not return for follow-up visits as scheduled. Grade 4 OM was seen in 2 patients at level 4. One patient in level 4 had delay in OM resolution. Overall, 4 of 15 patients never developed OM(Table 3). The response to treatment at 1 year is shown in Table 4. Median duration of follow-up for patients was 16.5 months (range, 3–44 months). Of the 14 patients, 5 patients showed CR at 1 year. Two of those patients received melphalan 160 mg/m^2 (level 2), 2 patients received 180 mg/m^2 (level 3), and 1 patient received 200 mg/m^2 (level 4). Six patients have received maintenance therapy after the transplantation (Table 4).

Non-Evaluable Group

Four patients were considered nonevaluable because they did not receive all 6 doses of palifermin. The first patient enrolled in level 1 developed asymptomatic grade 3 amylase elevation after the first 3 doses of palifermin and was taken off the study as the palifermin was stopped. This patient later developed grade 3 OM during the hospital stay. Protocol was later amended to allow administration of palifermin to patients with asymptomatic amylase/lipase elevation. The second nonevaluable patient enrolled in level 1 received 5 of the planned 6 doses of palifermin. The day +1 dose was accidently missed. This patient developed grade 1 OM. The third patient enrolled in level 3 received 5 doses of palifermin and developed grade 2 rash, grade 2 genital edema, and fluid retention. The patient refused the sixth dose of palifermin and had grade 1 OM during the hospital stay. The fourth nonevaluable patient in level 4 developed grade 3 infection after the first 3 doses of palifermin and, therefore, ASCT was delayed. The patient subsequently received melphalan 200 mg/m^2 in divided doses and did not develop any OM. Median duration of hospital stay for nonevaluable patients was 14.5 days (12–23). Grade 3 skin rash was observed in 1 patient. Grade 4 asymptomatic amylase elevation was seen in 1 patient and grade 3 tachycardia was seen in 1 patient. This patient also had grade 3 dyspnea and grade 4 congestive heart failure. No other severe toxicity was noted in this group.

Safety

All patients were monitored for adverse effects related to melphalan and palifermin up to day 100 after ASCT. Thirteen patients developed a skin rash. Grade 1 skin rash was seen in 3 patients and grade 2 was seen in 10 patients. Nine patients showed elevation of amylase. Grade 1 was seen in 3 patients, grade 2 in 3 patients, and grade 3 was seen in 3 patients. Elevated lipase was seen in 2 patients. One patient had grade 1 and the other had grade 2 lipase elevation. Diarrhea was seen in 12 patients. One patient had grade 3 diarrhea and was also positive had a *Clostridium difficile* infection. Eight patients had grade 1 diarrhea, and 3 patients had grade 2 diarrhea. Of the patients with grade 2 diarrhea, 1 was also positive for *Clostridium difficile*. Nine patients (60%) required narcotics; 4 patients needed total parenteral nutrition/nasogastric feeding. Seven patients had vomiting during the stay. Grade 1 vomiting was seen in 5 patients and grade 2 in 2 patients. One of 3 patients in level 2 developed atrial fibrillation on day +9. The patient had a known history of atrial fibrillation. Five of 15 patients were found to have positive blood cultures during the hospitalization (Table 5).

One patient in level 4 developed delayed OM recovery. This patient had grade 3 OM until day +53. A biopsy was performed of the lesion on her tongue, which was consistent with pyogenic granuloma. She received evoxac for treatment of the lesion. One patient in level 4

developed secondary graft failure, had multiple infections, and died at day +74. This patient was >65 years old and had received a prior ASCT for MM.

DISCUSSION

Patients with CKD are mostly excluded from clinical trials using high-dose chemotherapy due to increased morbidity and mortality and are thus denied the beneficial effects of ASCT. Melphalan has a log-linear effect on MM and a high-dose melphalan can possibly increase the antimyeloma activity. High-dose melphalan is associated with severe OM, which is more significant in patients with CKD [2,3,5,13,24]. The Food and Drug Administration recommends decreasing the intravenous melphalan dose by 50% in patients with BUN ≥30 mg/dL. Sirohi et al. [3] evaluated glomerular filtration rate as a surrogate marker of the outcome in patients treated with melphalan 200 mg/m^2 and noted a 71% incidence of severe OM. Badros et al. [13] in 2001 reported a 67% grade 2 or higher OM in patients with serum creatinine >2 mg/dL treated with melphalan 140 mg/m^2. Therefore, they recommended using a melphalan dose of 140 mg/m^2. Our study has demonstrated that the melphalan dose can be safely and effectively increased up to 180 mg/m^2 in patients with creatinine clearance ≤60 mg/mL. We were successful in controlling OM with palifermin, which is a major DLT observed in patients with RI [2,3,5,13,24].

The incidence of severe OM observed in our study was better as compared to other studies reported in patients with RI. The Kobbe et al. [23] study used palifermin 60 mcg/kg for 3 days before ASCT and observed an incidence of severe OM to be 64% in patients with creatinine clearance<50 mL/minute, despite the melphalan dose of 140 mg/m^2. This difference could be explained by more frequent doses of palifermin administered to our patients. We used palifermin 60 mcg/kg/day for a total of 6 days. Mucosal barrier injuries in the form of OM can play a significant role in development of infections in neutropenic patients [25–28]. Patients with RI have a higher incidence of such complications. Sirohi et al. [3] noted an incidence of 47% of ≥ grade 3 infections in patients with low glomerular filtration rate who were treated with high-dose melphalan. Using palifermin could lead to lower rates of infection and sepsis in such patients by preventing the mucosal barrier. In our study, documented bacteremia was observed in 5 of 15 patients (33%). Three of these 5 patients had severe OM. One patient in level 4 had grade 4 OM and grade 3 infections, which finally resulted in death. The patient's creatinine clearance was 31 mL/minute. This patient was >65 years old and had received a prior ASCT. Melphalan 200 mg/m^2 resulted in higher toxicity, including severe OM and treatment-related mortality, which led us to decrease the dose back to 180 mg/m^2 in the next cohort.

Most of our patients encountered the common side effects of palifermin, including white coating of the tongue, rash, edema, elevated amylase, and lipase, which are manifestations of its physiological action [29]. No grade 4 toxicity related to palifermin was noted. One of our patients developed delayed mucositis recovery, and she continued to have a lichenoid growth on the tongue that was not present before the treatment. This area on the lateral border of the tongue was biopsied and showed prominent granulation tissue with acute inflammatory infiltrate compatible with pyogenic granuloma. This may be from palifermin use, but a definite conclusion cannot be made.

Response to treatment was a secondary objective in our study and follow-up was restricted to 100 days posttransplantation, but the patients were still followed off protocol and we have reported the response at 1 year. Two of four patients who received 180 mg/m^2 showed complete response at 1 year. Because some of the patients were also started on maintenance therapy after 100 days, it is hard to attribute their responses to the benefits of the treatment beyond 100 days. As far as the benefit of dose escalation is concerned, there is a clear

advantage demonstrated in single and tandem ASCT trials in patients with myeloma with normal renal function. The rationale for dose reduction in patients with myeloma with RI is predominantly opted to reduce toxicity. In the absence of randomized trials, it is difficult to confirm or negate the therapeutic advantages for this strategy to improve response rate and survival. Results from single-center studies have conflicting results for melphalan dose ranging between 140 and 200 mg/m^2. Our study is probably the first attempt to study this group in a prospective format. This issue should be evaluated in a cooperative group setting in a randomized study.

After reviewing the medical charts of the 4 patients who were nonevaluable because they did not receive all 6 doses of palifermin, we found that severe OM was seen in 1 patient and the other 3 developed grade 1 or no mucositis at all. This finding could be explained by the fact that the patient who developed severe mucositis had a low creatinine clearance 20 mL/minute, whereas the other 3 had a creatinine clearance >50 mL/minute.

Palifermin permitted dose escalation of melphalan up to 180 mg/m^2 with acceptable toxicity in patients with CKD. This has the potential for further improving the outcomes of patients with myeloma who have abnormal renal function with single ASCT. Augmented cell kill may be achieved in such patients with doses of melphalan above what has been given historically without palifermin, thus overcoming the present-day barriers of DLTs in ASCT. The usefulness of palifermin could be further enhanced by using it in conjunction with other modalities such as oral cryotherapy, which by itself has been shown to reduce the severity of OM in patients undergoing ASCT [30]. In this small, prospective, randomized study, 3 of 21 patients (14%) in the cryotherapy group developed grade 3 to 4 OM compared to the 14 of 19 patients in the normal saline group. Melphalan 200 mg/m^2 dose was used as conditioning. Status of the renal function at the time of ASCT is not summarized, which makes the comparison with patients with RI difficult.

The primary objective of our dose-finding trial was to determine the MTD of melphalan in patients with RI who underwent ASCT for myeloma when treated with palifermin to prevent OM. A larger magnitude phase 2 trial is necessary to better evaluate the antimyeloma efficacy of this regimen.

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References

1. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. Eur J Haematol. 2000; 65:175–181. [PubMed: 11007053]
2. San Miguel JF, Lahuerta JJ, García-Sanz R, et al. Are myeloma patients with renal failure candidates for autologous stem cell transplantation? Hematol J. 2000; 1:28–36. [PubMed: 11920166]
3. Sirohi B, Powles R, Kulkarni S, et al. Glomerular filtration rate prior to high-dose melphalan 200 mg/m(2) as a surrogate marker of outcome in patients with myeloma. Br J Cancer. 2001; 85:325–332. [PubMed: 11487259]
4. Tricot G, Alberts DS, Johnson C, et al. Safety of autotransplants with high-dose melphalan in renal failure: a pharmacokinetic and toxicity study. Clin Cancer Res. 1996; 2:947–952. [PubMed: 9816255]

5. Knudsen LM, Nielsen B, Gimsing P, Geisler C. Autologous stem cell transplantation in multiple myeloma: outcome in patients with renal failure. Eur J Haematol. 2005; 75:27–33. [PubMed: 15946307]
6. Kyle RA, Rajkumar SV. Treatment of multiple myeloma: a comprehensive review. Clin Lymphoma Myeloma. 2009; 9:278–288. [PubMed: 19717377]
7. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med. 1996; 335:91–97. [PubMed: 8649495]
8. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol. 2005; 23:9227–9233. [PubMed: 16275936]
9. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003; 348:1875–1883. [PubMed: 12736280]
10. Bladé J, Rosiñol L, Cibeira MT, Rovira M, Carreras E. Hematopoietic stem cell transplantation for multiple myeloma beyond 2010. Blood. 2010; 115:3655–3663. [PubMed: 20203260]
11. Samuels BL, Bitran JD. High-dose intravenous melphalan: a review. J Clin Oncol. 1995; 13:1786–1799. [PubMed: 7602368]
12. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. Blood. 2002; 99:731–735. [PubMed: 11806971]
13. Badros A, Barlogie B, Siegel E, et al. Results of autologous stem cell transplant in multiple myeloma patients with renal failure. Br J Haematol. 2001; 114:822–829. [PubMed: 11564069]
14. Keefe DM, Sonis ST, Bowen JM. Emerging drugs for chemotherapy-induced mucositis. Expert Opin Emerg Drugs. 2008; 13:511–522. [PubMed: 18764726]
15. Schuster MW, Shore TB, Harpel JG, et al. Safety and tolerability of velafermin (CG53135-05) in patients receiving high-dose chemotherapy and autologous peripheral blood stem cell transplant. Support Care Cancer. 2008; 16:477–483. [PubMed: 17710442]
16. Spencer A, Horvath N, Gibson J, et al. Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. Bone Marrow Transplant. 2005; 35:971–977. [PubMed: 15778725]
17. Phillips GL, Meisenberg B, Reece DE, et al. Amifostine and autologous hematopoietic stem cell support of escalating-dose melphalan: a phase I study. Biol Blood Marrow Transplant. 2004; 10:473–483. [PubMed: 15205668]
18. Rubin JS, Osada H, Finch PW, Taylor WG, Rudikoff S, Aaronson SA. Purification and characterization of a newly identified growth factor specific for epithelial cells. Proc Natl Acad Sci U S A. 1989; 86:802–806. [PubMed: 2915979]
19. Blijlevens N, Sonis S. Palifermin (recombinant keratinocyte growth factor-1): a pleiotropic growth factor with multiple biological activities in preventing chemotherapy- and radiotherapy-induced mucositis. Ann Oncol. 2007; 18:817–826. [PubMed: 17030544]
20. Meropol NJ, Somer RA, Gutheil J, et al. Randomized phase I trial of recombinant human keratinocyte growth factor plus chemotherapy: potential role as mucosal protectant. J Clin Oncol. 2003; 21:1452–1458. [PubMed: 12697866]
21. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med. 2004; 351:2590–2598. [PubMed: 15602019]
22. Booth D, Potten CS. Protection against mucosal injury by growth factors and cytokines. J Natl Cancer Inst Monogr. 2001; (29):16–20. [PubMed: 11694560]
23. Kobbe G, Bruns I, Schroeder T, et al. A 3-day short course of palifermin before HD Treduces toxicity and need for supportive care after autologous blood stem-cell transplantation in patients with multiple myeloma. Ann Oncol. 2010; 21:1898–1904. [PubMed: 20233744]

24. Grazziutti ML, Dong L, Miceli MH, et al. Oral mucositis in myeloma patients undergoing melphalan-based autologous stem cell transplantation: incidence, risk factors and a severity predictive model. Bone Marrow Transplant. 2006; 38:501–506. [PubMed: 16980998]
25. Ruescher TJ, Sodeifi A, Scrivani SJ, et al. The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. Cancer. 1998; 82:2275–2281. [PubMed: 9610710]
26. Lark RL, McNeil SA, Vander Hyde K, et al. Risk factors for anaerobic bloodstream infections in bone marrow transplant recipients. Clin Infect Dis. 2001; 33:338–343. [PubMed: 11438899]
27. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol. 2001; 19:2201–2205. [PubMed: 11304772]
28. Blijlevens NM, Donnelly JP, De Pauw BE. Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for hematological malignancy: an overview. Bone Marrow Transplant. 2000; 25:1269–1278. [PubMed: 10871732]
29. Pierce G, Yanagihara D, Klopchin K, et al. Stimulation of all epithelial elements during skin regeneration by keratinocyte growth factor. J Exp Med. 1994; 179:831–840. [PubMed: 7509362]
30. Lilleby K, Garcia P, Gooley T, et al. A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2006; 37:1031–1035. [PubMed: 16633359]

Table 1

Who Oral Mucositis Assessments Scale

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Soreness and erythema	Erythema, ulcers, ability to eat solids	Ulcers, requires liquid diet	Alimentation not possible

The following was used as guidance in the oral mucositis assessments:

Grade 1 may include buccal mucosal scalloping with or without erythema. No ulcers. Patient can swallow solid diet.

Grade 2 may include ulcers with or without erythema. Patient can swallow solid diet.

Grade 3 may include ulcers with or without (extensive) erythema. Patient is able to swallow liquid, but not solid diet.

Grade 4 mean mucositis to the extent that alimentation is not possible. If total parenteral nutrition was started for reasons other than mucositis, a determination of the subject's ability to swallow must be made using the above criteria.

Table 2

Patient Characteristics

	No. of Patients (%)
Male gender	8 (53)
Median age (range)	59 (36–67)
White race	12 (80)
Median creatinine clearance, mL/minute (range)	42.8 (29–60)
CKD staging	
Stage 2	1 (7)
Stage 3	13 (87)
Stage 4	1 (7)
Stage 5	0
Durie-Salmon staging	
Stage III B	8 (53)
Stage III A	0
Stage III, creatinine at the time of diagnosis not available	4 (27)
Stage II B	3 (20)
Isotypes	
IgG kappa	5 (33)
IgG lambda	3 (20)
IgA kappa	2 (13)
IgD lambda	1 (7)
Kappa light chain	3 (20)
Lambda light chain	1 (7)
Previous treatment regimen	
One regimen	5 (33)
Two regimen	10 (67)
Previous BMT	2 (13)
Karnofsky Performance Score	
70	1 (7)
80	7 (47)
90	7 (47)
Disease status at the time of transplantation	
VGPR	3 (20)
PD	5 (33)
CR	4 (27)
PR	3 (20)
SD	0
Days in the hospital (range)	16 (12–74)
Median follow-up in months for those who were alive at day 100 (range)	16.5 (3–44)

CKD indicates chronic kidney disease; BMT, bone marrow transplant; VGPR, very good partial response; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

A <50 % reduction in serum M-protein, or if the patient has light chain disease only, a <50% reduction in the urine M-protein (Bence Jones Protein).

Table 3

Assessment of Oral Mucositis

Patients	WHO-OM Score Range	Duration of Severe OM (Grade 3+4)	Days to Resolution of OM
Level 1 – M 140			
1	2–3	4	15
2	0	0	0
3	1–2	0	23
Level 2 – M 160			
4	1	0	4
5	1–3	5	14
6	0	0	0
Level 3 – M 180			
7	1–3	3	12
8	1–2	0	14
9	1–3	6	15
10	1–3	17	28+
11	1–3	7	15
12	0	0	0
Level 4 – M 200			
13	0	0	0
14	1–4	7	25
15	1–4	42	28+

WHO indicates World Health Organization; OM, oral mucositis; M, melphalan.

Table 4

Disease Status

Dose of Melphalan	Disease Status at Transplantation	Disease Status at 100 Days	Disease Status at 1 Year
140	PD	SD	PR
140	VGPR	SD	SD
140	VGPR	SD	BMT
160	CR	CR	CR
160	PR	SD	CR
160	CR	CR	REL
180	PD	CR	CR
180	CR	CR	CR
180	PR	BMT	BMT
200	CR	REL	CR
200	PD	EXP	EXP
200	PR	PD	VGPR
180	PD	PR	PD
180	PD	PR	X
180	VGPR	VGPR	X

PD indicates progressive disease; SD, stable disease; PR, partial response; VGPR, very good partial response; BMT, bone marrow transplant; CR, complete response; REL, Relapse; EXP, deceased.

Response and progression in this study were evaluated using the Southwest Oncology Group (SWOG) criteria for Multiple Myeloma staging.

Table 5

Adverse Effects

	Adverse Effects			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Skin rash	3	10	0	0
Elevated amylase	3	3	3	0
Elevated lipase	0	1	11	0
Vomiting	5	2	0	0
Nausea	11	3	0	0
Diarrhea	8	3	1	0