A 3-day short course of palifermin before HDT reduces toxicity and need for supportive care after autologous blood stem-cell transplantation in patients with multiple myeloma


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Background: We retrospectively determined whether a 3-day short course of palifermin could reduce the toxicity of high-dose therapy (HDT) and autologous blood stem-cell transplantation (ASCT) in patients with multiple myeloma (MM).

Patients and methods: Sixty-seven consecutive patients received 80 μg/kg palifermin for 3 days before HDT with melphalan 200 or 140 mg/m² for patients with renal failure (group A). Granulocyte colony-stimulating factor (G-CSF) was applied after ASCT. Data on haematopoietic reconstitution and toxicity were compared with two previously published patient groups from our institution who had received pegfilgrastim but not palifermin (group B, n = 21) and patients who had received neither palifermin nor G-CSF (group C, n = 21).

Results: In group A, patients with renal failure had a significantly higher risk for severe mucositis (64% versus 16%, \( P < 0.002 \)). Patients with normal renal function who received palifermin experienced significantly less days of hospitalisation (\( P < 0.05 \)) and less need for narcotic analgesia (\( P < 0.05 \)), parenteral nutrition (\( P < 0.05 \)) and erythrocyte transfusions (\( P < 0.05 \)) in comparison with groups B and C. Time to haematopoietic reconstitution was not compromised by the use of palifermin.

Conclusions: In conclusion, a short 3-day course of palifermin may be able to reduce the toxicity of HDT and ASCT in patients with MM. Patients with impaired renal function at the time of HDT need additional strategies to further reduce the incidence of severe mucositis.

Key words: high-dose therapy, multiple myeloma, palifermin, pegfilgrastin, stem-cell transplantation

Introduction

High-dose therapy (HDT) and autologous blood stem-cell transplantation (ASCT) is the treatment of choice for patients <65 years with multiple myeloma (MM) because it prolongs disease-free survival and overall survival in comparison with conventional chemotherapy [1, 2]. Although supportive care has improved significantly during recent years, still a significant number of patients experience severe organ toxicity during ASCT.

In post-transplantation interviews, 42% of patients reported oral mucositis being the most debilitation transplantation-associated side-effect [3]. But severe mucositis is not the only condition that causes patient discomfort and pain. Patients who develop severe mucositis require more medical support in terms of narcotic analgesia, parenteral nutrition and time of hospitalisation. In addition, disruption of the mucosal barrier is an important risk factor for severe infections during neutropenia. Rapoport et al. showed that patients with severe mucositis following HDT were at a higher risk for culture-proven systemic infections than patients who were less severely affected by mucosal toxicity. As a consequence, severe mucositis in the context of haematopoietic stem-cell transplantation is a risk factor for increased morbidity, higher costs and treatment-related death [4–6].

Several factors influence the incidence of mucositis during stem-cell transplantation. The most important are diagnosis, type of transplant and type of conditioning regimen [7]. In a study by Spielberger et al. [8] in patients with various haematologic malignancies, the incidence of severe mucositis was 98% following conditioning with total body irradiation (TBI) in combination with high-dose etoposide and cyclophosphamide. In contrast, high-dose melphalan is
associated with severe mucositis in 20%–45% of patients with MM [9, 10]. In a previous study from our institution, we found an overall incidence of grade III–IV mucositis of 27% in patients receiving high-dose melphalan. The rate of severe mucositis increased to 80% when the conditioning regimen was augmented with idarubicin and cyclophosphamide [5].

Palifermin, a recombinant human keratinocyte growth factor, was approved in the European Union in October 2005 for prophylactic use to prevent severe mucositis in patients receiving HDT and ASCT. Since then, data have been presented showing that palifermin reduces mucositis among patients receiving allogeneic stem-cell transplantation as well as patients receiving intensive mucotoxic chemotherapy for lymphoma or colon cancer [11–14]. We here report for the first time clinical experience with a prophylactic 3-day short course of palifermin before high-dose melphalan and ASCT in patients with MM.

patients and methods
patients and treatment protocol
During a 3-year period from October 2005 to October 2008, we treated 92 consecutive patients with MM with a 3-day short course of i.v. palifermin at a dose of 60 μg/kg before HDT and ASCT. Palifermin was given as a single i.v. bolus injection on an outpatient basis on days −7, −6 and −5. Patients were admitted to hospital on day −4 and received a central catheter as well as prophylactic hydration. Melphalan was given at a cumulative dose of 100–200 mg/m² on days −3 and −2 depending on patient age and renal function.

The present analysis was restricted to patients who received their first or second autotransplant and were treated with either 200 mg/m² or 140 mg/m² melphalan in the case of a creatinine clearance <50 ml/min (group A, n = 67). Patients who received lower doses of melphalan for other reasons (e.g., age) were excluded from the analysis (n = 25). Following autologous blood stem-cell infusion on day 0, patients received granulocyte colony-stimulating factor (G-CSF) (pegfilgrastim n = 62, conventional G-CSF n = 5) to enhance haematopoietic reconstitution.

This group of patients was compared with similar patient groups with MM that had been reported previously by our group to analyse the effect of pegfilgrastim on haematopoietic reconstitution and supportive care after HDT and ASCT [15]. Patients who had received pegfilgrastim (group B, n = 21) had been treated from November 2004 to October 2005 and were compared with a matched-pair group (group C, n = 21) from our transplant database. The evolution of the treatment protocol is shown in Figure 1, groups A–C. Details on patient characteristics are given in Table 1.

supportive care
All patients gave written informed consent for HDT and were treated at the Department of Haematology, Oncology and Clinical Immunology of the Heinrich Heine University Duesseldorf according to treatment protocols approved by the local ethics committee.

All patients received identical supportive care including oral ciprofloxacin and i.v. aciclovir except for the use of palifermin and G-CSF as indicated above. Parenteral narcotic analgesia, usually using a patient-controlled analgesia pump, was introduced on an individual basis when patients reported pain that was not sufficiently controlled with novaminsulfone or paracetamol. Intravenous antibiotic therapy was started when patients experienced the first episode of fever >38.5°C or showed an increase in c-reactive protein indicative for systemic infection. Antimycotic drugs were added when persistent fever or results of clinical investigations indicated the presence of a mycotic infection. Parenteral nutrition was introduced when patients reported the inability for oral food intake for >2 days, irrespective of the reasons being mucositis, nausea or others.

Mucositis was scored once daily by the responsible physician and reported according to World Health Organisation (WHO) guidelines while patients were hospitalised [16]. Scoring of mucositis was not part of an oral care protocol.

Criteria for discharge were identical in all patients and included white blood cell (WBC) reconstitution (WBC >1 × 10⁹/l), independence from platelet transfusions, parenteral antibiotic or antimiycotic therapy, narcotic analgesia and nutrition.

data collection and statistical analysis
Data on patients’ characteristics, treatment, toxicity and supportive care were extracted retrospectively from patient charts by experienced medical personnel. The following parameters were assessed in an univariate analysis: days in hospital, days with i.v. narcotic analgesia, days with parenteral nutrition, days with i.v. antibiotic drugs, days with i.v. antimiycotic drugs, days with fever, number of erythrocyte and platelet transfusions, time to WBC recovery and time to platelet recovery. Data on incidence and severity
Table 1. Patient’s characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A No growth factor</th>
<th>Group B Pegfilgrastim</th>
<th>Group C Palifermin and G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>21</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>53 (42–64)</td>
<td>57 (39–69)</td>
<td>57 (39–69)</td>
</tr>
<tr>
<td>Sex, male : female</td>
<td>12 : 9</td>
<td>9 : 12</td>
<td>36 : 31</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>10</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>CD34+ / kg x 10⁶</td>
<td>3.9 (2–13)</td>
<td>4.5 (2–12)</td>
<td>3.2 (1.8–18)</td>
</tr>
<tr>
<td>First : second</td>
<td>18 : 3</td>
<td>18 : 3</td>
<td>51 : 16</td>
</tr>
</tbody>
</table>

G-CSF, granulocyte colony-stimulating factor.

Longer in patients with renal failure (median 9 days, range 6–43 versus median 7 days, range 4–11, P < 0.05).

Looking at the patients within the palifermin group, those with severe mucositis spent more days in hospital (median 19 days, range 16–49 versus median 17 days, range 13–39, P < 0.05) and needed more supportive care in terms of parenteral narcotics (median 5 days, range 0–14 versus median 0 days, range 0–17, P < 0.0001), i.v. antibiotics (median 8 days, range 0–37 versus median 5 days, range 0–24, P < 0.01) and parenteral nutrition (median 9 days, range 0–29 versus median 0 days, range 0–20, P < 0.01). There was a difference in the number of days with fever (median 1 day, range 0–13 versus median 0 days, range 0–17, P < 0.01) but no significant differences in the need for red blood cell or platelet transfusions. These findings show that mucosal damage is an important factor for secondary indicative parameters describing morbidity, supportive care and costs.

intergroup comparison

The palifermin group spent a median of 18 days in hospital (range 13–49 days). This was significantly less than the group of patients who had received pegfilgrastim but not palifermin (median 21 days, range 15–24, P < 0.05) and the group of patients who had received neither palifermin nor pegfilgrastim (median 22 days, range 15–29, P < 0.05). In addition, patients who had been given palifermin and G-CSF had less need for parenteral narcotic analgesia (median 0 days, range 0–17) than patients treated with pegfilgrastim (median 4 days, range 0–21, P < 0.05) or patients who had received no growth factor at all (median 8 days, range 0–21, P < 0.05).

The combination of palifermin and G-CSF tended to also reduce the days with parenteral nutrition but the difference was not statistically significant. There was no difference in the number of days with i.v. antibiotics and antimycotics, the latter being to few to be relevant in the setting of autologous haematopoietic stem-cell transplantation. The same was true for the need for red blood cell and platelet transfusions. Data on days in hospital and supportive care are given in detail in Table 2.

As mentioned above, patients with a reduced creatinine clearance <50 ml/min had a high incidence of severe mucositis of 64% despite the use of palifermin although the melphalan dose was reduced to 140 mg/m². We therefore analysed parameters indicative for regimen-related toxicity separately among patients with normal renal function.
In patients with normal renal function, differences between groups became even more prominent (Table 3). Palifermin prophylaxis and G-CSF support (group A) reduced days in hospital \( (P < 0.002) \), parental narcotics \( (P < 0.01) \), parenteral nutrition \( (P < 0.01) \) and need for erythrocyte transfusions \( (P < 0.01) \) in comparison with groups B (pegfilgrastim only) and C (neither palifermin nor G-CSF). Moreover, in comparison with group C, the number of days with fever was also significantly reduced (median 0 days, range 0–3 versus median 1 day, range 0–5, \( P < 0.05 \)).

Table 2. Clinical parameters for all patients

<table>
<thead>
<tr>
<th></th>
<th>n = 21</th>
<th>n = 21</th>
<th>n = 67</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group C</td>
<td>Group B</td>
<td>Group A</td>
</tr>
<tr>
<td>Days (median) to WBC &gt; ( 1 \times 10^9/l )</td>
<td>15 (11–29)</td>
<td>11 (9–14) ( ^a )</td>
<td>11 (8–23) ( ^b )</td>
</tr>
<tr>
<td>Days (median) to PLT &gt; ( 20 \times 10^9/l )</td>
<td>13 (9–49)</td>
<td>12 (8–20)</td>
<td>12 (7–21)</td>
</tr>
<tr>
<td>Median number of platelet concentrates</td>
<td>2 (0–11)</td>
<td>2 (0–11)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>Median number of red blood cell concentrates</td>
<td>2 (0–6)</td>
<td>2 (0–14)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>Days (median) with Fever</td>
<td>1 (0–5)</td>
<td>0 (0–5)</td>
<td>0 (0–13)</td>
</tr>
<tr>
<td>i.v. antibiotics</td>
<td>6 (0–23)</td>
<td>4 (0–21)</td>
<td>6 (0–37)</td>
</tr>
<tr>
<td>i.v. nutrition</td>
<td>6 (0–16)</td>
<td>6 (0–16)</td>
<td>0 (0–29)</td>
</tr>
<tr>
<td>i.v. narcotic analgesia</td>
<td>8 (0–21)</td>
<td>4 (0–21)</td>
<td>0 (0–17) ( ^c )</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>22 (15–29)</td>
<td>21 (15–34)</td>
<td>18 (13–49) ( ^c )</td>
</tr>
<tr>
<td>Median maximal mucositis (WHO)</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>Grade I (0–IV)</td>
</tr>
<tr>
<td>Median duration of mucositis, days</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>3 (0–43)</td>
</tr>
</tbody>
</table>

Mucositis grade and duration and secondary parameters of supportive care that are a reflection of toxicity among patients with multiple myeloma receiving high-dose therapy and autologous haematopoietic stem-cell transplantation. Values given in parentheses represent the range.

\( ^a P < 0.05 \) for B versus C.

\( ^b P < 0.05 \) for A versus C.

\( ^c P < 0.05 \) for A versus B and A versus C.

G-CSF, granulocyte colony-stimulating factor; WBC, white blood cell; PLT, platelet count; WHO, World Health Organisation.

Table 3. Excluding patients with a glomerular filtration rate <50 ml/min

<table>
<thead>
<tr>
<th></th>
<th>n = 19</th>
<th>n = 17</th>
<th>n = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group C</td>
<td>Group B</td>
<td>Group A</td>
</tr>
<tr>
<td>Days (median) to WBC &gt; ( 1 \times 10^9/l )</td>
<td>15 (13–29)</td>
<td>10 (9–14) ( ^a )</td>
<td>11 (8–23) ( ^b )</td>
</tr>
<tr>
<td>Days (median) to PLT &gt; ( 20 \times 10^9/l )</td>
<td>13 (9–49)</td>
<td>11 (8–18)</td>
<td>12 (7–21)</td>
</tr>
<tr>
<td>Median number of platelet concentrates</td>
<td>2 (0–11)</td>
<td>2 (0–4)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>Median number of red blood cell concentrates</td>
<td>2 (0–6)</td>
<td>2 (0–6)</td>
<td>1 (0–6) ( ^c )</td>
</tr>
<tr>
<td>Days (median) with Fever</td>
<td>1 (0–5)</td>
<td>0 (0–5)</td>
<td>0 (0–3) ( ^b )</td>
</tr>
<tr>
<td>i.v. antibiotics</td>
<td>5 (0–23)</td>
<td>2 (0–16)</td>
<td>5 (0–24) ( ^a )</td>
</tr>
<tr>
<td>i.v. nutrition</td>
<td>6 (0–16)</td>
<td>7 (0–16)</td>
<td>0 (0–20) ( ^c )</td>
</tr>
<tr>
<td>i.v. narcotic analgesia</td>
<td>8 (0–21)</td>
<td>4 (0–21)</td>
<td>0 (0–17) ( ^c )</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>21 (15–29)</td>
<td>19 (15–32)</td>
<td>17 (13–39) ( ^c )</td>
</tr>
<tr>
<td>Median maximal mucositis (WHO)</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>Grade 1 (0–IV)</td>
</tr>
<tr>
<td>Median duration of mucositis, days</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>1 (0–11)</td>
</tr>
</tbody>
</table>

Mucositis grade and duration and secondary parameters of supportive care that are a reflection of toxicity among patients with multiple myeloma receiving high-dose therapy and autologous haematopoietic stem-cell transplantation. Values given in parentheses represent the range.

\( ^a P < 0.05 \) for B versus C.

\( ^b P < 0.05 \) for A versus C.

\( ^c P < 0.05 \) for A versus B and A versus C.

G-CSF, granulocyte colony-stimulating factor; WBC, white blood cell; PLT, platelet count; WHO, World Health Organisation; ns, not significant.

discussion

To the best of our knowledge, this is the first single centre study showing that in patients with MM, a short course of palifermin before high-dose melphalan significantly reduces treatment-related toxicity following autologous blood stem-cell transplantation.

MM is the most common indication for HDT and autologous haematopoietic stem-cell transplantation in Europe \[17\]. Several studies have proven superiority of this treatment...
modality over conventional chemotherapy [1, 2]. With the development of treatments that introduce ‘new’ compounds like bortezomib or immunomodulatory drugs into classical chemotherapy regimens, the superiority of the high-dose approach may be questioned [18–20]. Given that today the mortality of HDT is not higher than that of conventional or modern combination chemotherapy protocols, issues of patient convenience, morbidity and economic aspects become even more important. One major drawback of HDT and ASCT is a higher incidence of severe organ toxicity, namely mucositis and infection, which are closely related [6, 21, 22]. Efforts to reduce severe mucositis induced by high-dose melphalan have been numerous; however, so far only oral cryotherapy has been shown to achieve some clinical benefit [23, 24]. Despite its cost-effectiveness, some disadvantages, especially insufficient compliance and the fact that cryotherapy cannot reliably be applied to deeper mucosal surfaces like the oesophagus, have limited its widespread use [10, 25, 26].

Palifermin, a humanised form of keratinocyte growth factor that is produced in Escherichia coli through recombinant DNA technology, has been approved by the Food and Drug Administration and by the European Medicines Agency to prevent severe mucositis in the context of HDT and haematopoietic stem-cell transplantation [27]. So far, no reports on the use of palifermin to prevent oral mucositis in patients with MM have been published.

The original phase II dose-finding study for palifermin was carried out in 129 patients with haematologic malignancies. In this study, three doses of palifermin (60 µg/kg) preconditioning and six doses of palifermin (pre- and postconditioning) were compared with placebo [28]. The incidence and severity of severe mucositis were significantly less in patients receiving palifermin. However, with a mean duration of mucositis of 5 and 4 days, the difference between three and six doses of palifermin was not statistically different. In view of a trend towards a higher efficacy, the six-dose schedule was tested in further trials like the final phase III trial that led to the approval of palifermin [8]. These early studies used a very intensive radiation-based conditioning regimen which is associated with an extremely high rate of WHO grades III and IV mucositis of 98%.

In an attempt to reliably assess the frequency and duration of severe mucositis in patients with MM who traditionally are treated with high-dose melphalan only, a prospective oral mucositis audit was carried out in 25 centres of the European Group for Blood and Marrow Transplantation [10]. This study found a rate of 46% of WHO grades III and IV mucositis in patients with MM after conditioning with high-dose melphalan which is somehow higher than the previously reported rate of 21%–27% [5, 9].

These findings indicate that careful education of physicians and nurses as well as standardisation of reporting procedures is required to evaluate mucositis as a reliable study end point [29]. On the other hand, secondary parameters like hospital stay, use of i.v. narcotic analgesia, parenteral nutrition and infection have been closely linked to mucosal damage in many studies and can be a good estimate of transplant morbidity [5, 6, 21, 22]. We therefore decided to retrospectively evaluate these parameters as a reflection of the impact of a 3-day short course of palifermin pre-transplantation on the toxicity of high-dose melphalan.

We chose to use only three doses of palifermin pre-transplant in view of the results of the phase II study by Spielberger et al. and the fact that high-dose melphalan is much less mucotoxic than TBI-based combination regimens. The high costs of palifermin are an additional argument for the use of a 3-day outpatient short course in this setting. Furthermore, a 3-day course of low dose (40 µg/kg) palifermin had a very favourable toxicity profile and efficiently reduced mucositis in patients receiving fluorouracil-based chemotherapy for metastatic colon cancer [14, 30].

Among the patients treated with palifermin, we found severe mucositis in 24%. The median duration of severe mucositis was 9 days (range 4–43 days). This compares favourably with the recently published results of the European Group for Blood and Marrow Transplantation prospective mucositis audit, where 46% of patients with MM experienced grades III and IV mucositis after melphalan at a dose of 200 mg/m² [10]. However, as our study was retrospective and less well controlled, this comparison is difficult. For further analysis, we chose two well-defined internally matched control groups that were well documented and recently published [15]. Still comparison of mucosal damage itself among the controls was not possible because documentation of mucositis in patient charts was insufficient in the past.

We observed that patients who developed mucositis despite treatment with palifermin had a longer stay in hospital and needed more i.v. narcotic analgesia and parenteral nutrition than patients without or with only moderate mucosal damage.

When we compared these secondary parameters of the palifermin group with those of the historical control groups who had only received pegfilgrastim or no growth factors after transplantation, we found a significant and clinical relevant advantage for the palifermin group in terms of hospital stay and use of i.v. narcotic analgesia. These findings were especially prominent in patients with normal renal function and reflect a marked reduction in toxicity which we and others could not achieve by the administration of myeloid growth factors alone [15]. The differences in the use of parenteral nutrition were less striking, most likely because nausea and vomiting rather than oral mucositis were the reason for parenteral nutrition in a significant number of patients. Oral cryotherapy has also been shown to reduce oral mucositis in patients treated with high-dose melphalan. Success was most prominent in the reduction of pain reported in patient questionnaires. However, the duration of hospital stay was not significantly reduced in a well-designed study from Seattle [23]. It would be interesting to compare or even combine cryotherapy and palifermin in patients treated with high-dose melphalan.

Still some patients had severe mucositis despite prophylactic treatment with palifermin which poses the question if higher doses of the drug would be even more effective. In this context, special attention has to be made to patients with renal failure. Among our patients, severe mucositis occurred in 64% of patients with a creatinine clearance <50 ml/min. In these patients, the duration of severe mucositis was 9 days (range 6–43 days). Among the patients with normal renal function who received 200 mg/m² melphalan, the rate of severe mucositis was only 16% and the median duration was 7 days.
(range 4–11 days, $P<0.05$). Several authors have reported a higher incidence of mucositis in this patient group as well as a need for more intensive supportive care and probably even higher treatment-related mortality [9, 31–34].

So far, there have been no reports on the use of palifermin in patients with renal impairment. Our data clearly show that a short 3-day course of palifermin before HDT does not prevent severe mucositis in patients with renal failure. However, results of a recent study in volunteers with renal impairment indicate that palifermin pharmacokinetics are not altered by renal function and argue for an intensified dosing schedule in patients with renal failure who receive HDT [35].

In the light of our findings, we indicate that a 3-day short course of palifermin may be sufficient to reduce treatment-related toxicity associated with severe mucositis in the majority of patients with MM treated with high-dose melphalan. If confirmed in a multicentre prospective study, that is currently ongoing in transplant centres throughout Europe, this may lead to a change in the standard of care (http://www.clinicaltrials.gov/ct2/show/NCT00434161).

disclosures

GK, RH, UG and RF have received speakers’ honoraria from Amgen.

references

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