Use of palifermin for the prevention of high-dose methotrexate-induced oral mucositis


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Background: Oral mucositis is a frequent problem after high-dose methotrexate (HD-MTX), impairing patient’s quality of life, leading to higher rates of infections and delaying subsequent chemotherapy. This report describes the effect of palifermin in patients treated within the GMALL-B-ALL 2002 protocol containing HD-MTX who developed a severe mucositis in cycle A1/B1.

Patients and methods: Ten patients, all with World Health Organization grades III–IV oral mucositis in cycles A1/B1, obtained palifermin with subsequent similar or identical cycles to reduce mucositis. Thus, patients serve as their own control for efficacy of palifermin.

Results: All 10 patients developed grades III–IV mucositis in cycles A1/B1 without palifermin, whereas only two of 10 developed grades III–IV mucositis in corresponding cycles A2/B2 with palifermin. Only four of 10 patients showed infections in the cycles with palifermin compared with 10 of 10 patients without palifermin. The duration of mucositis in patients who acquired a higher grade mucositis despite treatment with palifermin could be reduced from 12.9 days (median) without to 11 days with palifermin. The amount of i.v. opioid analgetics could be significantly reduced.

Conclusion: Palifermin might reduce the incidence, severity and duration of oral mucositis in HD-MTX-based chemotherapy and may influence clinical sequelae such as infection and quality of life.

Key words: methotrexate, oral mucositis, palifermin

Introduction

Oral mucositis is a severe and frequent adverse effect of high-dose methotrexate (HD-MTX)-based chemotherapy. It is caused by damage of the mucosal lining of the gastrointestinal tract (GIT) as a result of a dynamic series of biological events involving different cellular and tissue compartments of the GIT mucosa. Understanding of the pathobiology has increased rapidly during the last years [1–5]. Mucosal barrier injury is based on a network of interactions involving the endothelium, extracellular matrix, metalloproteinases, submucosal reactions and connective tissue [1–3]. Sonis and coworkers developed a pathophysiological model dividing the dynamical process of mucositis in five phases: initiation, up-regulation, signal amplification, ulceration and healing [2, 3].

Oral mucositis and myelosuppression represent dose-limiting toxicity effects of HD-MTX. Mucositis is associated with an increased risk of life-threatening infections [6, 7], with the need for total parenteral nutrition, i.v. analgetic therapy, and may lengthen hospital stay with increased economic burden and consumption of health care resources [8–11]. Oral mucositis impairs the patient’s quality of life by pain, the inability to eat, swallow and talk. For many patients with grades III–IV mucositis, the subsequent cycle of chemotherapy is delayed. A grade IV mucositis is an emergency situation in oncology, ethically demanding to relieve the patient’s situation. The recent evidence-based management guidelines from the Multinational Association of Supportive Care in Cancer [12] make several recommendations to provide a better patient comfort including good oral hygiene, oral decontamination with antibacterial and antifungal mouthwash and topical and systemic pain management.

Numerous substances have been used in addition to treat oral mucositis such as ice chips [13, 14], antioxidants as glutamine, N-acetylcysteine, benzylamine hydrochloride and antiinflammatory agents like prostaglandine E1 and E2 [15]. Until now none of them has proven an unequivocal clinical benefit.

Palifermin is a recombinant human keratinocyte growth factor (KGF) which is known to stimulate growth of epithelial cells in a wide variety of tissues. In murine models, a beneficial effect on mucositis could be shown [16]. In December 2004, the Food and Drug Administration approved palifermin (recombinant KGF from Escherichia coli, Amgen, Thousand Oaks, CA, USA) on the basis of randomized data showing...
a decrease of incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem-cell support [17]. Therefore, the updated guidelines of the Multinational Association of Supportive Care in Cancer recommend the use of palifermin in patients who are receiving high-dose chemotherapy and total body irradiation with autologous stem-cell transplantation (level 1, grade A recommendation) [12]. KGF receptors are present on epithelial cells in many tissues including the tongue, buccal mucosa, salivary gland, esophagus, stomach, intestine, lung, liver, pancreas, kidney, bladder, mammary gland and eye lens as well as on tumor cells of different histology [18]. Receptors could not be found on lymphoma and lymphoblastic leukemia cell lines [18].

The mechanism of action of palifermin in mucositis is not completely elucidated. It leads to a down-regulation of proinflammatory cytokines [19] and increases antiinflammatory cytokines such as IL-13 [20, 21]. Palifermin protects the epithelium against reactive oxygen molecules by modifying the expression of detoxifying transcription factors and enzymes [22].

In this series, we observed patients who were treated in the GMALL-B-ALL/B-NHL 2002 protocol, which is based on HD-MTX and is used for certain aggressive B-cell lymphomas and lymphoblastic leukemias. The incidence of grades III–IV (World Health Organization, WHO, oral toxicity scale, Miller et al. [23]) mucositis upon HD-MTX within this protocol ranges from 56% (cycle A1) to 32% (cycle B1) as described by Hoelzer et al. [24]. Another study shows a mucositis rate of 42% [25]. The data of the B-NHL90 trial (GMALL study group) with 3 g MTX/m² (>55 years 500 mg MTX/m²²) showed a grade III (Donnelly scale) mucositis rate of 41%–54% in cycle A1 and 61%–75% in cycle B1. In previous trials (B-NHL 83, B-NHL 86), mucositis grades I–IV were observed in 50%–53% of chemotherapy cycles [26].

All patients reported here developed a severe mucositis in cycle A1 or B1. In order to prevent additional mucositis, these patients received palifermin for the corresponding following cycles of similar or identical chemotherapy. Thus, patients in this retrospective series can serve as their own control for efficacy of palifermin in preventing mucositis.

**patients and methods**

**patients**

We report on a retrospective series of 10 patients with B-cell acute lymphoblastic leukemia (B-ALL) and aggressive B-cell lymphoma classified according to the WHO classification. Patients’ characteristics are given in Table 1. We have included only patients into this report who developed severe mucositis in initial treatment cycle A1 or B1 without palifermin and were then given palifermin in the subsequent treatment cycles.

**treatment protocol**

The patients were treated from September 2004 to March 2007 on protocol GM-ALL-B-ALL/B-NHL 2002 (upon approval by ethical board and written informed consent) and developed severe mucositis. The protocol outline with age-related dose modifications is depicted in Figure 1. Two of 10 patients were treated in the protocol for patients >55 years of age with a slightly reduced MTX dosage (500 mg/m² compared with 1500 mg/m²). One patient was treated in the ‘elderly protocol’.

Eight of 10 patients received a ‘run-in’ therapy (prephase) of 5 days with prednisone 60 mg/m² and cyclophosphamide 200 mg/m² before the cycle A1. Two patients with mediastinal B-cell non-Hodgkin’s lymphoma (B-NHL) did not receive any prephase therapy.

Patients with mucositis in cycle A1 or B1 received prophylaxis and supportive treatment including morphine, tetracaine, panthenol and camomile-containing mouthwashes, oral hygiene and amphotericin B suspensions to prevent intestinal candidosis. All patients received recombinant granulocyte colony-stimulating factor (G-CSF) to shorten the time of grade IV neutropenia. Prophylactic oral hygiene, amphotericin B and G-CSF were not changed during the subsequent cycles.

**grading of mucositis**

Mucositis grade was judged daily by the four-point WHO scale [23]. The observation was carried out by the authors and, to ensure uniformity of judgment, by the first and the last author during the time of mucositis maximum. All these patients developed severe WHO grades III–IV oral mucositis in the cycle A1 (seven of 10) or B1 (three of 10). One of these patients (number 9, Table 1) did not get MTX in cycle A1 because of a surgical bowel intervention.

**palifermin application**

Because of their mucositis, all 10 patients obtained palifermin (Kepivance™, Amgen) for 3 days before and another 3 days after the following corresponding chemotherapy cycle (A2 or B2) to reduce the risk of further higher grade mucositis. Prior written informed consent was obligatory. Palifermin dose was 60 μg/kg/day, which is the full dose recommended or a lower daily dose as outlined in Table 1.

**results**

Figure 2A and B depicts the maximum grade of mucositis observed in chemotherapy cycles A1/B1 without palifermin versus A2/B2 with palifermin support. Evaluated together, there were 16 episodes of severe grade IV and one grade III mucositis in the chemotherapy cycles without palifermin support. In contrast, we have observed only one episode of grade IV, four episodes of grade III and four episodes of grade II mucositis during the chemotherapy cycles with palifermin support (difference \( P < 0.05 \), Mann–Whitney–Wilcoxon test).

The amount of i.v. opioid analgetics could be reduced from a total of 2403 mg morphine in cycle A1 (3380 mg cycle B1) without palifermin to 640 mg in cycle A2 (480 mg cycle B2) with palifermin (difference \( P < 0.05 \), Mann–Whitney–Wilcoxon test). The intraindividual dose changes are presented in Figure 3A and B.

Furthermore, the duration of mucositis in patients who acquired a higher grade mucositis despite treatment with palifermin could be slightly reduced. The median duration of grade III/IV mucositis without palifermin was 12.9 days (16 cycles with mucositis) with a range from 7 to 18 days. The median duration of grades III–IV mucositis with palifermin was 11 days with a range from 10 to 13 days (not significant, Mann–Whitney–Wilcoxon test). In this evaluation, patients not developing severe mucositis under palifermin protection were not included.

Ten of 10 patients developed a severe infection in cycle A1 or B1 without palifermin. Severe infection is defined as fever (>38.5°C) in neutropenia which had to be treated with empiric systemic antibiotic therapy. In the palifermin-supported chemotherapy cycles, only four of 10 patients showed a severe
Table 1. Patients treated in the GMALL-B-ALL/B-NHL 2002 protocol (severe infection is defined as body temperature >38.5°C and use of systemic antibiotics)

<table>
<thead>
<tr>
<th>Patient ID No.</th>
<th>Diagnosis</th>
<th>Maximum grade of mucositis (WHO) Without palifermin</th>
<th>Maximum grade of mucositis (WHO) With palifermin</th>
<th>Dosage of palifermin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B-ALL</td>
<td>Grade IV, A1, 12 days;</td>
<td>Grade I A2–C2 10 days</td>
<td>A2 60 µg/kg bodyweight (BW); B2 and C2 30 µg/kg BW</td>
</tr>
<tr>
<td>2</td>
<td>Burkitt-like lymphoma</td>
<td>Grade IV, A1, 15 days;</td>
<td>Grade II, B1, 9 days;</td>
<td>A2–C2 60 µg/kg BW;  B1 30 µg/kg BW</td>
</tr>
<tr>
<td>3</td>
<td>Mediastinal B-NHL</td>
<td>Grade IV B1, 15 days;</td>
<td>Grade II C1, 4 days</td>
<td>A2–C2 60 µg/kg BW; C1 30 µg/kg BW d=3 to =1; 60 µg/kg BW d1–3 after chemotherapy</td>
</tr>
<tr>
<td>4</td>
<td>Mediastinal B-NHL</td>
<td>Grade IV A1, 10 days;</td>
<td>Grade I A2</td>
<td>A2–C2 30 µg/kg BW</td>
</tr>
<tr>
<td>5</td>
<td>B-ALL</td>
<td>Grade IV A1, 13 days;</td>
<td>Grade II cycle B2, 5 days</td>
<td>A2–C2 30 µg/kg BW</td>
</tr>
<tr>
<td>6</td>
<td>Burkitt lymphoma</td>
<td>Grade II, A1, 4 days;</td>
<td>Grade I, A2, 6 days;</td>
<td>A2 ~40 µg/kg BW; B2–C2 ~50 µg/kg BW</td>
</tr>
<tr>
<td>7</td>
<td>Atypical Burkitt lymphoma</td>
<td>Grade IV B1, 12 days;</td>
<td>Grade III, A2, 10 days;</td>
<td>A2–B2, 60 µg/kg BW; protocol could not be finished because of infectious complications</td>
</tr>
<tr>
<td>8</td>
<td>B-ALL, elderly protocol</td>
<td>Grade IV A1, 16 days;</td>
<td>Grade II B1/B2, 3 days;</td>
<td>~40 µg/kg BW B1–B3</td>
</tr>
<tr>
<td>9</td>
<td>Burkitt lymphoma</td>
<td>Grade IV B1, 12 days;</td>
<td>Grade III C1 13 days;</td>
<td>60 µg/kg BW</td>
</tr>
<tr>
<td>10</td>
<td>B-ALL</td>
<td>Grade IV A1, 14 days;</td>
<td>Grade I A2–C2, 7 days;</td>
<td>60 µg/kg BW C1–C2</td>
</tr>
</tbody>
</table>

Infection. Interestingly, infection is associated with a higher grade mucositis.

Since cycles A1 and A2 contain identical (with the exception of the run-in phase of corticosteroids and cyclophosphamide given to eight of 10 patients before A1) and cycles B1 and B2 contain identical chemotherapy, patients can serve as their own controls for the antimucositis efficacy of palifermin. Figure 4 documents the maximum appearance of mucositis in three patients at identical times following chemotherapy cycles without (part A, C and E) or with palifermin (part B, D and F) support. Only three individual cycle comparisons for two patients (numbers 7 and 9, Figure 2, Table 1) did not show an improvement of mucositis severity by palifermin. Patient number 10 did receive palifermin in cycle C1, but showed a grade III mucositis. However, in the corresponding cycle C2, a mucositis of only grade I was observed.

As we report on an individual patient series, there was some variation in the course of supportive palifermin treatment concerning individual cases and these are depicted in Table 1.

Discussion

We report descriptive observation data from 10 patients who were treated in the trial protocol GM-ALL-B-ALL/NHL 2002 or the respective protocol for elderly patients (one patient) and developed severe mucositis. In summary, we observed a considerable effect of palifermin reducing the dosage of i.v. morphine, severity, duration and clinical sequelae (such as infection) of mucositis when similar (A1/A2) or identical (B1/B2) chemotherapy cycles without palifermin support were compared with those with palifermin support in identical patients.

Recently, palifermin has been described to reduce the prevalence and severity of oral mucositis in patients with hematologic malignancies undergoing high-dose therapy with autologous peripheral blood stem-cell transplantation [17]. However, there are also standard chemotherapy regimens not requiring stem-cell support, which can be associated with severe mucositis. In a placebo-controlled phase II study published recently, it was demonstrated that palifermin is
effective in reducing the incidence of oral mucositis in patients with metastatic colorectal cancer undergoing 5-fluorouracil/calcium folinate chemotherapy [27]. In contrast to these data, a recently published Cochrane review about 'Interventions for preventing oral mucositis for patients with cancer receiving treatment' by Worthington et al. [28] on the basis of three randomized trials [17, 29, 30] shows that there is no statistically significant difference between palifermin/repifermin and placebo. It was concluded that recombinant KGF could not be supported or refuted as more or less effective than placebo due to insufficient evidence. However, HD-MTX-based chemotherapy is well known to be associated with high mucositis rates and MTX-based chemotherapy regimen was not included in the Cochrane review [28]. This opens the possibility that there might be a stronger mucositis-preventive effect of palifermin in MTX-based chemotherapy.

Figure 1. Prephase: cyclophosphamide 200 mg/m² d1–5, prednisone 60 mg/m² d1–5. Cycle A1/A2: rituximab 375 mg/m² d7 (A2 d77); dexamethasone 10 mg/m² d8–12 (A2 d78–82); vincristine 2 mg d8 (A2 d78); MTX 1500 mg/m² (500 mg/m² > 55 years) d8 (A2 d78); ifosfamide 800 mg d8–12 (A2 d78–82); cytarabine 2 × 150 mg/m² d11–12 (A2 d81–82); VP16 100 mg/m² d11–12 (A2 d81–82); cytarabine 40 mg i.t.h. d8, 12 (A2 d78, 82); MTX 15 mg i.t.h. d8, 12 (A2 d78, 82); dexamethasone 4 mg i.t.h. d8, 12 (A2 d78, 82). Cycle B1/B2: rituximab 375 mg/m² d28 (B2 d98); dexamethasone 10 mg/m² p.o. d29–33 (B2 99–103); vincristine 2 mg d29 (B2 d99); MTX 1500 mg/m² (500 mg/m² > 55 years) d29 (B2 d99); cyclophosphamide 200 mg/m² d29–33 (B2 99–103); cytarabine 25 mg/m² d32–33 (B2 d102–103); cytarabine 40 mg i.t.h. d29, 33 (B2 d99, 103); MTX 15 mg i.t.h. d29, 33 (B2 d99, 103); dexamethasone 4 mg i.t.h. d29, 33 (B2 d99, 103). Cycle C1/C2: rituximab 375 mg/m² d49 (C2 d119); dexamethasone 10 mg/m² p.o. d50–54 (C2 120–124); vindesine 3 mg/m² maximum 5 mg d50 (C2 120); MTX 1500 mg/m² (500 mg/m² > 55 years) d50 (C2 d120); VP16 250 mg/m² d53–54 (C2 d123–124); cytarabine 2 × 2 g/m² (2 × 1 g/m² > 55 years) d54 (C2 d124). Protocol for elderly patients: Prephase: cyclophosphamide 200 mg/m² d1–5, prednisone 60 mg/m² d1–5. Cycle A1/A2/A3: rituximab 375 mg/m² d7 (A2 d49, A3 d98); dexamethasone 10 mg/m² d8–12 (A2 d50–54, A3 99–103); MTX 500 mg/m² d8 (A2 d50, A3 99); ifosfamide 400 mg d8–12 (A2 d50–54, A3 99–103); cytarabine 2 × 60 mg/m² d11–12 (A2 d53–54, A3 d102–103); VP16 60 mg/m² d11–12 (A2 d53–54, A3 d102–103); MTX 12 mg i.t.h. d8 (A2 d50, A3 99). Cycle B1/B2/B3: rituximab 375 mg/m² d28 (B2 d77, B3 d119); dexamethasone 10 mg/m² p.o. d29–33 B2 78–82, B3 120–124; vincristine 1 mg d29 (B2 d78, B3 d120); MTX 12 mg i.t.h. d29 (B2 d78, B3 120).

Figure 2. (A) Maximum grade mucositis with and without palifermin in cycles A1 versus A2 (P < 0.05, Mann–Whitney–Wilcoxon test). Numbers in circles refer to patients as given in Table 1. Patient 9 did not receive MTX during cycle A1. (B) Maximum grade mucositis with and without palifermin in cycles B1 versus B2 (P < 0.05, Mann–Whitney–Wilcoxon test). Numbers in circles refer to patients as given in Table 1. Patient 2 received palifermin in cycle B1.
The cases reported here receiving HD-MTX provide evidence that palifermin might reduce the risk of oral mucositis and its severe side-effects such as infections. Our data lead to the suggestion that the effect is due to palifermin. In cycle A1, the incidence of mucositis could be increased by the application of the run-in therapy. Therefore, it cannot be completely excluded that the decrease in mucositis rate is partly caused by the absence of the run-in therapy in the subsequent cycles. This, however, is not the case in cycles B1 and B2, where treatment is identical. Furthermore, it seems theoretically possible that single patients may tolerate subsequent cycles of chemotherapy with a less severe mucositis than the first cycle. This, however, is not in line with our experience treating patients in the time before accessibility of palifermin. With two exceptions (both obtaining the run-in treatment in the first cycles), every patient had a benefit with a reduction in mucositis grade and also shown by the amount of opioid analgetics given during the mucositis period. Having used palifermin for a while in our department, patients started to actively ask for off-label use of this specific drug for mucositis prevention and refused HD-MTX-containing chemotherapy without. Furthermore, our observations suggest the possibility of a dose reduction for palifermin which should be further studied.

However, this is a report on a case series with retrospective evaluation and cannot replace prospective, controlled studies which should be carried out before the use of palifermin in HD-MTX regimen can be recommended as standard of care for mucositis prevention in HD-MTX chemotherapy.

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