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Similar effectiveness of Fomukal and Caphosol in oral mucositis treatment after allogeneic hematopoietic stem cell transplantation

Podobna skuteczność Fomukalu i Caphosolu w leczeniu zapalenia błony śluzowej jamy ustnej po allogenicznym przeszczepieniu macierzystych komórek krwiotwórczych

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Objective: Oral mucositis occurs in 75% to 100% of allogeneic HSCT recipients can cause pain, facilitate infections, delay discharge, and threaten life. The aim of the study was to evaluate prophylaxis with the remineralizing mouthwash solution of supersaturated calcium phosphate rinse (SCPR) with Fomukal on measures of severity of mucositis and consequent interventions and complications, in comparison to Caphosol, already evaluated post-transplant.

Materials/Methods: In this prospective, randomized, non-inferiority trial, 46 patients undergoing allogeneic HSCT were equally randomized to Fomukal or Caphosol, each administered four times daily from initiation of conditioning until the granulocyte count ≥0.2 G/L. Hematologist measured the daily severity of mucositis according to a WHO scale and patients self-assessed its symptoms. Need for analgesics, anti-infectious drugs, total parenteral nutrition (TPN) and incidence of complications were also assessed.

Results: Fomukal vs. Caphosol groups had the same all following indicators: median measures of WHO oral mucositis reduction (0 vs. 2; P = NS), length of disease course (0 vs. 6 days; P = NS), peak and mean mouth (1 vs. 2; P = NS and 0.06 vs. 1; P = NS) and throat pain (1 vs. 1; P = NS and 0.22 vs. 0.31; P = NS), and peak and mean swallowing problems (1 vs. 1; P = NS and 0.19 vs. 0.25; P = NS). Analgesics need (7 vs. 10 patients; 0 vs. 0 days; P = NS) and the need for antifungals (1 vs. 2 drugs; P = NS) were not different, while the need for antibiotics and antivirals (3.5 vs. 5 drugs; P = 0.011 and 1 vs. 2 drugs; P = 0.023) were lower in the Fomukal group. Measures of complications: infections (7 vs. 12 patients, P = NS) and a GVHD (13 vs. 14 patients, P = NS, grade 1 vs. 1, P = NS) did not differ.

Discussion: Both SCPR mouth rinses, Fomukal and Caphosol, were associated with similar effectiveness in reducing severity of oral mucositis.

Keywords: **oral mucositis, calcium phosphate, hematopoietic stem cell transplantation**

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INTRODUCTION

Oral mucositis (OM) is the most common early complication of hematopoietic stem cell transplantation (HSCT). The incidence of OM has been estimated to range from 75% to 100% of patients treated with high-dose chemotherapy and/or total body irradiation (TBI) before HSCT [5, 31, 33]. The understanding of pathophysiologic mechanisms of oral mucositis is increasing. Mucositis is a result of nonspecific toxic effects of radiation and/or chemotherapy on rapidly proliferating basal epithelial cells, submucosal cells, and endothelial cells, which results in clonogenic cell death, leading to mucosal ulceration, loss of mucosal integrity and microbiological colonization with subsequent further inflammation [10]. This occurs during post-therapeutic neutropenia, predisposing to viral, bacterial, and fungal infections. A five-phase model was described to demonstrate mucosal barrier injury, including initiation, gene up-regulation and generation of signal messengers, signal amplification, ulceration, and healing [27]. How the calcium and phosphate ions influence this process is unknown. Mucositis is responsible for painful ulcerations in the oral cavity, erythema, xerostomia, dysphagia, dysarthria, and life-threatening sepsis [28]. Mucositis may affect all functions of the mouth: drinking, eating, and speaking, which not only leads to impairment of nutrition and lower quality of life, but also may necessitate the use of total parenteral nutrition (TPN) and analgesics. It may also cause delayed discharge, interruption of treatment, increased costs and may increase risk of failure. Despite the use of standard oral hygiene regimens, mucositis is one of the most common causes of severe pain in allogeneic HSCT recipients [8]. Drugs considered most harmful to oral mucosa include busulfan, high dose melphalan, cyclophosphamide with TBI [2, 10] and use of methotrexate (MTX)-containing graft-versus-host-disease (GVHD) prophylaxis [4].

Mucositis can be described by several scales, but the most common is the World Health Organization (WHO) five--stage scale: 0 – no change; 1 – soreness/erythema; 2 – erythema, ulcers, patient can swallow solid food; 3 – ulcers, patient requires liquid diet only; and 4 – oral alimentation impossible. Strategies for preventing mucositis include basic oral hygiene, antioxidant drugs (glutamine, amifostine), inflammation and cytokines production inhibitors, physical strategies including oral cryotherapy and laser therapy [3, 5]. Positive effects have been obtained with interleukin-11, keratinocyte growth factor (KGF), granulocyte or granulocyte macrophage colony-stimulating factor [6, 9, 19, 20, 26]. Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) have developed guidelines, reflecting synthetic consensus of their authors on potential strategies for managing mucositis, but no guideline was possible related to the individual use of mouth rinses including calcium phosphate in patients receiving chemotherapy, due to inadequate and/or conflicting evidence. The guidelines should be viewed as fluid and will likely undergo changes as higher levels of evidence, which support or refute treatment, develop [14].

Supersaturated calcium phosphate – Caphosol (EUSA Pharma, Langhorne, PA) is an electrolyte mouth rinse used as artificial saliva, partially replacing ionic and pH balance within the oral cavity, which is used in addition to standard mucositis prophylaxis during high dose chemotherapy or radiatiotherapy. It has been tested in multiple, randomized, blinded trials, the results of which are controversial. In the part of reports Caphosol rinses did not reduce the incidence, duration or severity of mucositis associated with cancer treatment in patients undergoing chemotherapy, radiotherapy, autologous or allogeneic bone marrow transplantation [1, 3, 7, 13, 15, 24, 25, 30, 35]. Numerous other reports support the efficacy of Caphosol for an OM indication. Caphosol efficiently reduced the grade and/or duration of OM and associated pain in 24 out of 30 studies evaluating calcium-phosphate mouthwashes for OM prophylaxis and treatment [23].

Recently, the alternative aqueous mouthwash solution of supersaturated calcium phosphate-Fomukal (Vipharm SA, Poland) has became available. The statistically significant reduction in mean severity of xerostomia, OM, dysphagia, strong opioid consumption and frequency of prolonged hospitalization was reported after prophylaxis with Fomukal [12].

In the current study in patients undergoing allogeneic HSCT after high-dose chemotherapy and radiotherapy, we aimed to assess the effectiveness of Fomukal in comparison to Caphosol in its ability to prevent mucositis, reduce its duration and severity, reduce the need for TPN and analgesics, and improve patient comfort.

MATERIALS AND METHODS

Forty-six consecutive patients undergoing allogeneic HSCT in the transplant center in Katowice in 2018–2018 were included into this prospective, randomized, nonblinded controlled trial; half of the group received treatment

Table 1. Patient characteristics

Characteristic	Fomukal	Caphosol
Age (years) Mean (range)	48 (22–71)	47 (25–65)
Sex		
Men	9	13
Women	14	10
Regimen		
Busulfan	**11**	**11**
Busulfan (12.8 mg/kg), cyclophosphamide (120 mg/kg)	6	8
Busulfan (10 mg/kg), fludarabine (180 mg/m^2)	5	3
Total Body Irradiation	**5**	**6**
TBI (12 Gy), cyclophosphamide (120 mg/kg)	4	4
TBI (2 Gy), cyclophosphamide (120 mg/kg), fludarabine (150 mg/m^2)	1	2
Treosulfan	**6**	**6**
Treosulfan (30 g/m^2), fludarabine (150 mg/m^2)	4	6
Treosulfan (20 g/m^2), cyclophosphamide (160 mg/kg)	2	0
Other	**1**	**0**
Rituximab (375 mg/m^2, 3x1000 mg), fludarabine (90 mg/m^2), bendamustine (390 mg/m^2)	1	0
Source of transplant		
Matched sibling donor	6	6
Matched unrelated donor	17	15
Haploidentical donor	0	2
Diagnosis		
Acute myeloblastic leukemia	6	13
Acute lymphoblastic leukemia	4	5
Chronic myelomonocytic leukemia	1	3
Myelodysplastic syndrome	4	2
Myelofibrosis	2	0
Hodgkin lymphoma	2	0
Other (chronic myelogenous leukemia, chronic lymphocytic leukemia, severe aplastic anemia, multiple myeloma)	4	0

with Fomukal, and the remaining half with Caphosol. Local bioethical committee approved the study and written informed consent was obtained from all patients. Medications, immunosuppressive therapy, and antifungal, antibacterial, and antiviral agents given during granulocytopenia were similar between the two groups, without significant variation between them.

Fomukal and Caphosol each consist of two aqueous solutions (a phosphate solution and calcium solution). Combining both solutions in equal volumes prior to use forms a supersaturated solution with both calcium and phosphate ions. Fomukal solutions are separately packaged in two 225 ml bottles, Caphosol in two 15 ml plastic ampules. Fomukal and Caphosol active chemical components are identical.

Fomukal or Caphosol were administered within respective groups for rinsing mouths four times daily from the first day of conditioning until patients reached the absolute neutrophil count ≥0.2 G/L, a value that was considered to indicate the beginning of neutrophil recovery.

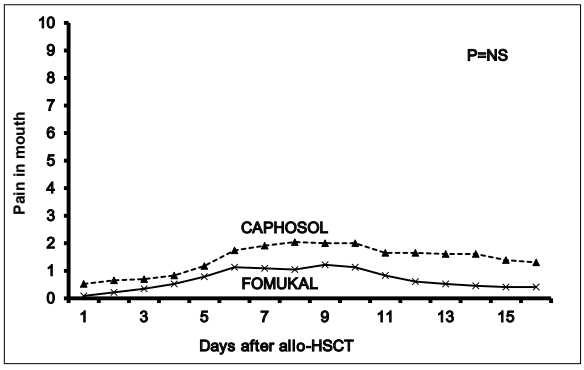
Patients were stratified into two equal groups according to age, conditioning regimen (busulfan, treosulfan, or TBI), and type of donor (either related or unrelated). The level of pain in the mouth and pharynx was self-assessed by patients with use of a 0–10 visual analog scale (VAS) and measured swallowing problems using a 0–5 VAS [22]. A physical examination of the oral cavity with rating of mucositis according to WHO scale was performed by the same experienced hematologist each day throughout the study. Statistical analysis included nonparametric Mann-Whitney U tests and Yates chi-square tests.

RESULTS

Mucositis was evaluated by an experienced physician using the WHO scale.

Three-fourths of the patients (34/46) were diagnosed with leukemia (acute myeloblastic leukemia, 19; acute lymphoblastic leukemia, 9; chronic myelomonocytic leukemia, 4; chronic myelogenous leukemia, 1; and chronic lymphocytic leukemia, 1; Table 1). The remainder was diagnosed with had myelodysplastic syndrome (six), myelofibrosis (two), Hodgkin lymphoma (two), multiple myeloma (one) and severe aplastic anemia (one). Almost half of the patients (22) had been on busulfan (10–12.8 mg/kg) and either cyclophosphamide (120 mg/kg) or fludarabine (150 mg /m^2), 11 had undergone irradiation (2 or 12 Gy) and

a.



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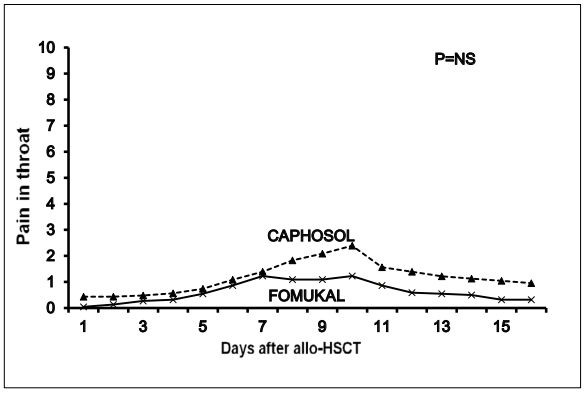

Fig. 1. Self-assessed [VAS 1-10] mean pain in mouth (a) and throat (b) in patients treated with Fomukal or Caphosol. VAS – Visual Analogue Scale, HSCT –Hematopoietic Stem Cell Transplantation

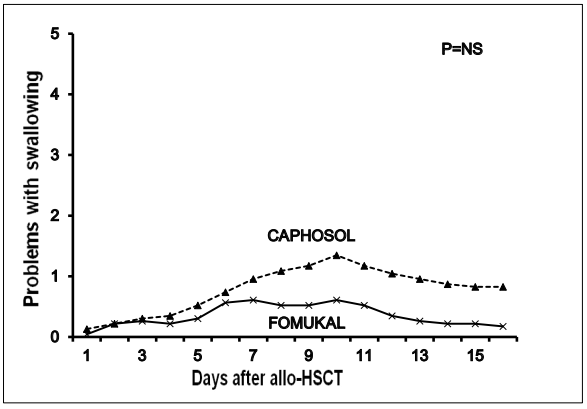

Fig. 2. Self-assessed [VAS 1-5] mean problems with swallowing in patients treated with Fomukal or Caphosol. VAS – Visual Analogue Scale, HSCT – Hematopoietic Stem Cell Transplantation

received cyclophosphamide (120mg/kg), and 12 received treosulfan (20–30 g/m^2) and either cyclophosphamide (160 mg/kg) or fludarabine (150 mg/m^2). One patient had received rituximab (375 mg/m^2+3x1000 mg), bendamustine (390 mg/m^2) and fludarabine (150 mg/m^2).

The median mucositis score for the Fomukal group was 0 and 2 for the Caphosol group (P=NS). The median duration of mucositis was 0 days for the Fomukal group and 6 days for the Caphosol group (P=NS). Throughout the course of mucositis, average mouth and pharynx pain intensity and problems swallowing were similar in the Fomukal group and in the Caphosol group (Figures 1, 2).

Measures of peak mean pain in the mouth, peak mean pain in the pharynx, and peak mean swallowing problems were also similar in both groups (Table 2). Days to an absolute neutrophil count of >0.5 G/L and to a platelet level >20 G/L were not significantly different between groups. Interventions required by mucositis and related complications are reported in Table 3. There was no difference in analgesics administration for mucositis-related pain (ketoprofen, fentanyl, metamizole, tramadol, and acetaminophen) between Fomukal and Caphosol groups (7 vs. 10 pts, P = NS; 0 vs. 0 days, P = NS; respectively). No difference was observed in infectious complications following allogeneic HSCT: 7 pts (30 %) vs. 12 pts (52 %), P = NS. Of the seven patients in the Fomukal group, five had bacterial infections (four with bacteremia), one had viral infection (cystitis Polyoma BKV), and one had a fungal infection (*C. krusei*). Of the twelve in the Caphosol group with infectious complications, five had bacterial infections (one with bacteremia), six had viral infections (five had cystitis Polyoma BKV), and one had a fungal infection (*P. jiroveci*). The median number of different antibiotics and antiviral drugs used in patients treated with Fomukal was lower than in patients treated with Caphosol (antibiotics: 3.5(1–7) vs. 5(2–7), P = 0.011; antivirals: 1(1–1) vs. 1(1–2), P = 0.023; respectively), there was no difference between groups in the variety of antifungals (1(1–4) vs. 2(1–4), P = NS). There was no difference in GVHD occurrence and severity between groups: GVHD occurred in 13 patients in the Fomukal group (GVHD involvement: eleven, skin only; one, skin and gut; one, upper part of gastrointestinal tract only) and in 14 patients in Caphosol group (ten, skin only; one, skin and gut; one, liver; two, skin, gut, and liver), P = NS; the median overall degree of acute GVHD was 1 vs. 1, P = NS. Both supersaturated rinses were well tolerated, no adverse events were observed, and no patient in either group withdrew early.

DISCUSSION

The development of mucositis in patients treated for malignancies not only significantly complicates their clinical course, but also has adverse economic consequences. With colleagues, we have previously reported the beneficial influence of Caphosol on reduction of mucositis symptoms in comparison with customary care-topical mouth solutions [17]. Caphosol reduced the incidence, severity, and duration of oral mucositis and shortened analgesic therapy requirement in patients who received BEAM conditioning [21, 34]. Caphosol was evaluated as a potentially effective treatment decreasing the incidence of chemotherapy – or radiation – induced OM [11, 18, 36]. The incorporation of mineral derivatives into prophylaxis of mucositis may decrease the incidence of peak OM after cytotoxic therapy [16].

Table 2. Measures of mucositis severity

Characteristics of mucositis and treatment	Fomukal*	Caphosol*	p
Severity (WHO scale)	0 (0–3)	2 (0–4)	0.075
Duration (days)	0 (0–14)	6 (0–24)	0.089
Peak mean pain in mouth (0–10 VAS)	1 (0–8)	2 (0–9)	0.222
Peak mean pain in pharynx (0–10 VAS)	1 (0–10)	1 (0–10)	0.296
Peak mean swallowing problems (0–5 VAS)	1 (0–5)	1 (0–5)	0.241
Days to absolute neutrophil count >0.5 G/L	16.5 (13–22)	16 (11–41)	0.822
Days to platelets > 20 G/L	12 (9–26)	12.5 (6–20)	0.712

Abbreviations: WHO, World Health Organization; VAS, visual analog scale

* Median (range)

Table 3. Interventions and complications

Interventions and complications	Fomukal	Caphosol	p
Analgesics (patients needing treatment)	7	10	0.365
Duration analgesics used (days)*	0 (0–12)	0 (0–18)	0.270
Acute GVHD (number of patients)	13	14	0.767
Degree of acute GVHD*	1 (0–2)	1 (0–3)	0.625
Infectious complications (number of patients)	7	12	0.139
Antibiotics (number of drugs used)*	3.5 (1–7)	5 (2–7)	0.011
Antifungals (number of drugs used)*	1 (1–4)	2 (1–4)	0.387
Antivirals (number of drugs used)*	1 (1–1)	1 (1–2)	0.023

* Median (range)

In this trial, 46 patients undergoing conditioning for HSCT were randomized into two groups of 23 each: one group received treatment with Fomukal and the other received Caphosol. Patients underwent both treatments four times daily for an average of 28.9 (range, 15–39) days post-transplantation. Cases of mucositis in both groups were not different in grade and duration and were associated with a similar degree of mouth, and throat pain, causing similar swallowing problems and requiring the same level of pain relief. The distinguishing feature of SCPR in comparison with other mouth rinses is the high concentration of Ca^{2+} and PO_4^{3-} ions leading to their diffusion into epithelial intercellular spaces preventing mucosal damage. The Ca^{2+} ions play a crucial role in the inflammatory process, the blood-clotting cascade, fibrin production, and tissue repair. The PO_4^{3-} ions also play an important biochemical role by facilitating intracellular signalling and regulating the voltage potential inside the cell, both important for repairing and protecting damaged mucosal surfaces [21].

While it seems unlikely that any anti-infective agent will prevent or delay damage to the basal cell layer caused by radiotherapy and chemotherapy, a potent anti-infective agent may help alleviate pain, shorten the period of mucositis, decrease the incidence of bacteremia/sepsis, and thus contribute to a lessening of morbidity and mortality [29]. The indications of SCPR mouthwash include its addition to standard prophylaxis and treatment of mucositis after cytotoxic therapy and reduction of dryness in oral cavity and throat, either temporary or permanent, which is often associated with pain.

The lack of double-blinding due to its impracticality is a limitation of the study. Although both supersaturated calcium phosphate solutions have to be mixed, Caphosol requires opening a single-use clear ampule and a blue ampule immediately before each administration, while Fomukal is provided in two bottles 225 ml each, which are being used during about one week. There was an observed lower number of days with use of antibiotics and antiviral drugs in the Fomukal group as compared to Caphosol group, but there was the same level of infectious complications in both groups. These results warrant confirmation in larger controlled, multicenter, randomized trials.

CONCLUSIONS

Compared with the Caphosol group, the Fomukal group showed at least noninferiority in mean and peak measures

of oral and throat toxicity reduction and showed similar oral mucositis pattern, indicating that in the trial reported here, both SCPR mouth rinses, Fomukal and Caphosol, were associated with similar effectiveness in reducing severity of oral mucositis.

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