Journal of BUON **17:** 363-368, 2012

ORIGINAL ARTICLE

A supersaturated calcium phosphate solution seems to effectively prevent and treat oral mucositis in haematopoietic stem cell transplanted cancer patients - single centre experience

A. Wasko-Grabowska, P. Rzepecki, S. Oborska, J. Barzal, B. Mlot, K. Gawronski, M. Wasko, C. Szczylik

Bone Marrow Transplantation Unit, Department of Oncology, Military Institute of Medicine, Warsaw, Poland

Summary

Purpose: *Oral mucositis (OM) is one of the most frequent and bothersome complications of high-dose chemotherapy with subsequent auto- and allogeneic haematopoietic stem cell transplantation (HSCT). We have assessed the effectiveness of supersaturated calcium phosphate rinse (Caphosol®) and palifermin (Kepivance®) in the prophylaxis of OM caused by HSCT.*

Methods: *Caphosol® and Kepivance® were prospectively evaluated in OM prophylaxis in 64 patients after HSCT and compared against themselves and an historical control group.*

Results: *Grade 3 and 4 OM was not observed in patients treated with Caphosol® and palifermin. None of those patients needed total parenteral nutrition (TPN), too. In the Caphosol® group 40.9% of the patients did not develop OM, and 70% of patients treated with palifermin were free of any kind of OM symptoms. In the control group OM was observed in all cases.*

Conclusion: *Caphosol® seems to decrease the incidence, severity and duration of OM, the demand for opioids and for TPN. It needs to be tested in randomized trials, because its easy administration and cost-effectiveness may render it a valuable addition to the standard care in the treatment of OM.*

Key words: caphosol, haematopoietic stem cell transplantation, oral mucositis, palifermin, supersaturated calcium phosphate rinse

Introduction

OM is a common complication of oncological treatments. It represents one of the most important dose-limiting toxicities of chemotherapy and occurs frequently after high-dose chemotherapy with subsequent auto- and allogeneic HSCT. It affects around 60-100% of patients undergoing preparatory regimes [1-4].

The occurrence and progression of OM (e.g. when assessed on a 5-grade WHO scale) puts the HSCT patients at higher risk of infection, additional medical procedures (parenteral nutrition and/or opioids) and prolonged hospital stay [5]. The infection caused by microorganisms from the oral cavity is the main cause of death among patients undergoing HSCT [6,7].

The risk factors for development of OM after autologous HSCT include previous radiotherapy, non-Hodgkin's lymphoma as the reason for the transplantation, using etoposide in chemotherapy for mobilizing the haematopoietic stem cells or in the preparatory regime before transplantation [8,9].

Hitherto, there has been no uniform standard of care in prophylaxis and treatment of OM [10,11]. In a clinical practice guidelines published in 2004, an expert panel recommended basic oral care, systemic and local anaesthetics/analgesics, low-level laser therapy and cryotherapy (in patients who are treated with bolus doses of 5-fluorouracil/ 5-FU or edatrexate) for OM prevention and treatment [11]. Since that time, one medication has gained a regulatory approval for the OM - a recombinant human protein that mimics endogenous growth factor for epithelial cells (KGF) - palifermin (Kepivance®). This agent proved to decrease the occurrence and duration of OM, as well as to alleviate the

Correspondence to: Anna Wasko-Grabowska, MD. Department of Oncology, Military Institute of Medicine, 128 Szaserow Street, 04-141 Warsaw, Poland. Tel: +48 226817819, +48 693321088, Fax: +48 226103098. E-mail: anna.wasko@autograf.pl

Received 28-07-2011; Accepted 09-10-2011

symptoms in patients receiving myeloablative therapy and requiring stem cell transplantation [12,13]. Based on palifermin trials' findings, in 2007 the updated MASCC/ISOO mucositis guidelines recommend this drug for the prevention of OM in autologous HSCT recipients conditioned with high dose chemotherapy and total body irradiation. Also cryotherapy is recommended for the prevention of OM in HSCT patients receiving high dose melphalan [14].

A new preparation has been recently registered, a supersaturated calcium phosphate solution - (trade name Caphosol®). It is used as a mouthwash in order to moisten and cleanse the oral cavity, including oral mucosa, tongue and the oropharynx. It is assumed that highly concentrated Ca^{2+} and PO_4^{3-} ions diffuse to the epithelium interstitial matrix and help maintaining mucosal integrity and healing the deficits [15].

In this study the 3-year single-institution experience with 3 OM treatment modalities in patients after high-dose chemotherapy with subsequent auto- and allogeneic HSCT (from a related donor) is being reported. We especially investigated whether Caphosol® is an effective mean to prevent and treat OM in HSCT cancer patients.

Methods

Patients

The study was conducted in the at the BMT Unit of the Department of Oncology, Military Institute of Medicine in Warsaw, Poland. A total of 84 patients were included. Patients treated with palifermin and Caphosol®, in addition to the standard oral care, were prospectively recruited. Data of patients treated with standard care were retrieved retrospectively. During the time of patients' recruitment into the two consecutive prospective groups, all Unit's patients were screened daily for study eligibility by one of the study coordinators, who were oncologists in charge on the bone marrow transplant unit. From 2005 to 2007, 20 patients with haematological malignancies were given palifermin therapy as an extension of their standard oral care. The results from that group have already been published [16]. Between January and December 2009, 44 adult patients received supersaturated calcium phosphate oral rinse in addition to the standard oral care. Another 20 subsequent patients, hospitalized from 2005 through 2006, constituted a historical group - they received a standard of care treatment and were daily followed for the development of mucositis as a part of the standard care protocol.

The institutional review board approved this study and all the patients from the prospective subgroups gave informed consent for their participation.

The protocol

All of the patients underwent a preconditioning protocol administered according to the standard practice, regardless of the OM prophylaxis. The auto- or allogeneic HSCT has been performed using stem cells from bone marrow and/or peripheral blood. All of the allogeneic transplants were obtained from the patients' siblings. The treatment did not diverge from universally accepted standards of care in patients having HSCT. Standard oral care, given to all of the patients, included topical fluoride rinses and prophylaxis of fungal, herpetic and *P. carinii* infections.

The independent variable was the treatment the patients received:

1. Palifermin (Kepivance®; Biovitrum, Stockholm, Sweden) - 60 mg/kg once daily i.v. for 3 consecutive days before and after conditioning therapy (total of 6 doses).

2. Supersaturated calcium phosphate solution (Caphosol®, EUSA Pharma Europe Ltd, Oxford, UK) - 4 times per day, each dose of 15 ml, beginning on the first day of the preparatory regime until discharge.

TPN was used according to the standard protocol.

Methods of measurement and definitions

OM was assessed using the 5-grade WHO oral toxicity scale [17]. OM was assessed on a daily basis, beginning at the start of the preparatory regime and continuing until discharge from hospital or death. In patients with suspected OM, the diagnosis was confirmed by a supervising researcher. Onset of OM indicated the first day of appearance of OM symptoms after HSCT. The duration of OM was defined as the time of OM symptoms after HSCT or until death. The patient records were prospectively analyzed with use of a standardized data-collection case report form to retrieve demographic and clinical data. All patients were followed until discharged from hospital by one of the study physicians and were monitored for the occurrence of any complications.

Statistical analysis

Dependent variables included the occurrence, duration and severity of OM and the number of days with opioid treatment. The baseline characteristics of the patients (age, diagnosis and conditioning regimens) were compared between the groups using one-way ANOVA test. Non-parametric tests for multiple independent samples (Kruskal-Wallis test and Mann-Whitney U test) were used to compare the groups for outcomes of interest - incidence of OM grades 1-4 and 3-4, the duration and severity of OM, TPN and opioid usage.

The statistical analysis was performed using the program Statistica 9.0, with a p value of <0.05 (for a two-sided test) considered significant.

Results

Comparison of baseline characteristics showed no statistical differences between all 3 groups (Table 1).

Addition of either Caphosol® or palifermin to the standard regimen decreased the overall incidence and the severity of OM, when compared with standard oral care ($p<0.01$ in both cases). Of note, 14 patients in the palifermin group and 18 patients in the Caphosol® group did not develop OM at all. Moreover, a significant reduction in the occurrence of grade 3 and 4 OM was observed (0% in both treated groups in comparison with

Table 1. Characteristics of patients in the palifermin, caphosol® and standard care (historical control) groups

No	*Age (years)*	*Disease*	*Type of transplantation*	*Conditioning regimen*	*Peak grade of mucositis (WHO)*	*Duration of mucositis (total, days)*	*Opioids used (days)*	*Study group*
1	45	ALL	allogeneic	TBI/VP-16	I	4	0	palifermin
2	52	AML	autologous	BuCy	0	0	0	palifermin
3	43	MM	allogeneic	Flu/LPAM	I	5	3	palifermin
4	47	CML	allogeneic	BuCy	0	0	0	palifermin
5	44	MDS	allogeneic	BuCy	0	0	0	palifermin
6	54	NHL	autologous	BEAM+rituximab	0	0	0	palifermin
7	53	AML	autologous	BuCy	0	0	0	palifermin
8	42	NHL	autologous	BEAM+rituximab	I	4	0	palifermin
9	28	NHL	autologous	BEAM+rituximab	I	5	3	palifermin
10	56	MM	autologous	LPAM	I	5	0	palifermin
11	53	MM	autologous	LPAM	0	0	0	palifermin
12	49	AML	allogeneic	BuCy	0	0	0	palifermin
13	59	NHL	autologous	BEAM	0	0	0	palifermin
14	49	HD	autologous	BEAM	0	0	0	palifermin
15	62	HD	autologous	BEAM	0	0	0	palifermin
16	22	NHL	allogeneic	Flu/treosulfan/alemtuzumab	0	0	0	palifermin
17	50	AML	allogeneic	Flu/treosulfan/alemtuzumab	0	0	0	palifermin
18	22	ALL	allogeneic	TBI/VP-16	I	4	0	palifermin
19	29	HD	autologous	BEAM	0	0	0	palifermin
20	22	NHL	allogeneic	Flu/treosulfan/alemtuzumab	0	0	0	palifermin
21	45	AML	allogeneic	BuCy	2	5	5	Caphosol®
22	42	AML	allogeneic	BuCy	2	6	6	Caphosol®
23	40	AML	allogeneic	BuCy	1	4	0	Caphosol®
24	39	AML	allogeneic	BuCy	1	5	0	Caphosol®
25	40	AML	allogeneic	BuCy	1	4	0	Caphosol®
26	39	AML	allogeneic	BuCy	1	4	0	Caphosol®
27	30	MDS	allogeneic	BuCy	1	5	0	Caphosol®
28	55	MDS	allogeneic	BuCy	1	5	0	Caphosol®
29	42	ALL	allogeneic	TBI/Cy	2	7	7	Caphosol®
30	33	ALL	allogeneic	TBI/Cy	1	4	0	Caphosol®
31	22	HD	allogeneic	TBI/Flu RIC	0	0	0	Caphosol®
32	23	HD	allogeneic	TBI/Flu RIC	0	0	0	Caphosol®
33	56	MM	autologous	Mel200	1	4	0	Caphosol®
34	53	MM	autologous	Mel200	1	5	0	Caphosol®
35	64	MM	autologous	Mel200	1	4	0	Caphosol®
36	39	MM	autologous	Mel200	0	0	0	Caphosol®
37	54	MM	autologous	Mel200	0	0	0	Caphosol®
38	53	MM	autologous	Mel200	0	0	0	Caphosol®
39	60	MM	autologous	Mel200	0	0	0	Caphosol®
40	58	MM	autologous	Mel200	1	4	0	Caphosol®
41	62	HD	autologous	BEAM	2	7	7	Caphosol®
42	49	HD	autologous	BEAM	2	6	6	Caphosol®
43	29	HD	autologous	BEAM	1	4	0	Caphosol®
44	22	HD	autologous	BEAM	1	5	0	Caphosol®
45	25	HD	autologous	BEAM	0	0	0	Caphosol®
46	30	HD	autologous	BEAM	0	0	0	Caphosol®
47	23	HD	autologous	BEAM	0	0	0	Caphosol®
48	29	HD	autologous	BEAM	0	0	0	Caphosol®
49	37	HD	autologous	BEAM	1	5	0	Caphosol®
50	33	HD	autologous	TreoMel	1	4	0	Caphosol®
51	23	HD	autologous	TreoMel	0	0	0	Caphosol®
52	42	NHL	autologous	BEAM	1	5	0	Caphosol®
53	28	NHL	autologous	BEAM	0	0	0	Caphosol®
54	59	NHL	autologous	BEAM	1	4	0	Caphosol®
55	22	NHL	autologous	BEAM	1	0	0	Caphosol®
56	54	NHL	autologous	BEAM	0	0	0	Caphosol®
57	28	NHL	autologous	BEAM	0	0	0	Caphosol®
58	24	NHL	autologous	BEAM	0	0	0	Caphosol®
59	32	NHL	autologous	TreoMel	0	0	0	Caphosol®
60	34	NHL	autologous	TreoMel	0	0	0	Caphosol®

Continued on next page

Continued from previous page

No	*Age (years)*	*Disease*	*Type of transplantation*	*Conditioning regimen*	*Peak grade of mucositis (WHO)*	*Duration of mucositis (total, days)*	*Opioids used (days)*	*Study group*
61	21	GCT	autologous	CarboVP16	1	4	0	Caphosol®
62	24	GCT	autologous	CarboVP16	2	6	0	Caphosol®
63	20	GCT	autologous	CarboVP16	1	4	0	Caphosol®
64	19	GCT	autologous	CarboVP16	0	0	0	Caphosol®
65	57	NHL	allogeneic	BEAM+ alemtuzumab	II	7	6	control
66	41	MDS	allogeneic	BuCy	II	9	10	control
67	54	HD	autologous	BEAM	II	10	10	control
68	23	NHL	autologous	BEAM	II	6	5	control
69	23	HD	autologous	BEAM	II	6	5	control
70	43	NHL	autologous	BEAM	II	6	4	control
71	40	NHL	autologous	BEAM	III	10	12	control
72	44	NHL	autologous	BEAM	II	10	11	control
73	25	ALL	allogeneic	TBI/VP+16	IV	18	22	control
74	24	MDS	allogeneic	Flu/LPAM/alemtuzumab	IV	12	14	control
75	47	MM	allogeneic	Flu/LPAM	IV	10	15	control
76	33	CML	allogeneic	BuCy	III	8	7	control
77	56	AML	autologous	BuCy	III	10	10	control
78	64	AML	autologous	BuCy	II	14	9	control
79	55	MM	autologous	LPAM	I	5	0	control
80	58	MM	autologous	LPAM	II	7	6	control
81	26	AML	allogeneic	BuCy	IV	12	15	control
82	22	NHL	allogeneic	Flu/LPAM	IV	15	17	control
83	56	AML	allogeneic	BuCy	IV	20	22	control
84	60	HD	autologous	BEAM	III	13	12	control
85	57	NHL	allogeneic	BEAM+alemtuzumab	II	7	6	control

AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia, HD: Hodgkin's lymphoma, NHL: non Hodgkin's lymphoma, MDS: myelodysplastic syndrome, MM: multiple myeloma. Conditioning regimens: VP-16 (etoposide), TBI: total body irradiation, Bu: busulphan, Cy: cyclophosphamide, Flu: fludarabine, LPAM: melphalan, BEAM- BCNU+ etoposide+ cytosine arabinoside

50% for the control group, $p<0.01$), as well as of the average time of OM duration (mean 10.4 days for the control group, 1.35 days for palifermin, and 2.73 days for Caphosol®; $p=0.02$ and 0.03, respectively).

In comparison with the historical control group, addition of any of the two preparations decreased significantly the requirement for opioids by shortening the period of their usage (mean duration of administration was 0.59 days for Caphosol®, 0.3 days for palifermin and 10.6 for the control group; $p<0.01$ for both comparisons).

Differences in OM incidence and duration were observed for all 3 groups, regardless of the type of transplantation. While comparing two prospectively evaluated treatment modalities, a significant difference was observed (Mann-Whitney U test, $p=0.02$) in the severity of OM for palifermin and Caphosol® - none of the patients treated with palifermin developed more than grade 1 OM, grade 2 OM developed in 13.6% of the patients treated with Caphosol®. However, no significant differences in overall occurrence and duration of OM or requirement for analgesics were observed between the groups treated with Caphosol® and palifermin ($p=1.0$).

No patient in the Caphosol® or palifermin groups required TPN and no adverse reactions were noted. One patient receiving Caphosol® expressed dislike for the taste of the preparation, though it did not lead to discontinuation of the rinse. In the historical group, more than a half (51%) of the patients required TPN.

Discussion

In this study we have shown that the addition of Caphosol® or palifermin to the standard oral care regimens leads to sustained improvement in clinical outcomes in HSCT transplant patients who are at risk of developing OM. Evidence of improved oral mucosa function is that until discharge of our HSCT patients (both allo- and autologous) who were given either Caphosol® or palifermin, the OM morbidity and severity were less compared with those treated with standard care treatment. The incidence of severe mucositis was markedly reduced compared to the control group. This was also reflected in the limited need for analgesics and no need for TPN. The effectiveness of Caphosol® in the prophylaxis of OM is comparable to the effectiveness of another medication, well acknowledged in OM therapy - palifermin [12,18]. None of the patients from both

groups developed grade 3 or 4 OM. The supersaturated calcium phosphate appeared to be inferior only in the reduction of the percentage of patients with advanced grades of OM. Who grade 2 OM was present in 13.6% of the patients taking Caphosol®, as compared to none in the palifermin group, with same total incidence of OM in both treatment groups. An advantage of Caphosol® is its ease of use as an oral rinse, which guarantees good patient compliance [19], and lack of any adverse reactions. The medication has also an excellent safety and pharmacoeconomic profile (Table 2).

So far, only one antimucositis agent - palifermin - has been proven to reduce the incidence, severity and duration of OM [18,20-23]. In 2004 Spielberger et al. published promising results of their phase III research, assessing the efficacy of palifermin in patients receiving high-dose chemotherapy with total body irradiation with subsequent HSCT. It has been stated that palifermin decreased the rates of occurrence and shortened the duration of acute OM, decreased the demands for narcotic analgesics and the duration of their usage and decreased the occurrence of neutropenic fever, duration of hospitalization and the necessity of TPN. All these results were statistically significant. Lower numbers of hematogenous infections were also observed, but without statistical significance [23].

The other now available agent is a supersaturated calcium phosphate rinse (Caphosol®). In 2003 Papas et al. published a results of a prospective randomized, double-blind clinical study, which demonstrated significant benefit using Caphosol® with standard oral hygiene in the treatment and prophylaxis of OM related to high-dose chemotherapy and radiotherapy [15].

Another point regarding the clinical course of our study and clinical practice in the future is worth noting. Palifermin is given in a total of 6 doses i.v., which requires the presence and supervision of qualified nursing personnel. This is not the case for Caphosol® which can be easily and safely self - administered throughout the treatment period. This advantage can be also used if Caphosol® was to be used for prolonged periods to reduce the OM linked to the *graft versus host* disease.

Some authors recommend other, non-medical treatment modalities for OM treatment, like oral cryotherapy (especially in patients receiving preparatory regimes with short half-life chemotherapeutics, e.g. like melphalan or 5-fluorouracil) or low-energy laser therapy. For the latter, though, limited access to expensive equipment and necessity of professional training of the team are the main obstacles [24-26]. The cost-effectiveness might play a role in a preferential choice of medical treatment too, as Caphosol® therapy, even if used throughout the whole hospital stay, is manyfold cheaper than palifermin (Table 2).

Table 2. Pharmacoeconomic profile of the palifermin, caphosol® and standard of care in Poland

Substance	*Duration of treatment (days)*	*Total cost of treatment per patient (in euros)*
Palifermin	6	6000
Caphosol	30	200
Standard care	50	100

Although the core of our research was conducted prospectively, its historic control group is an obvious limitation. Further research with randomization is necessary to establish a universal, successful and safe standard of care in such a common and bothersome complication as OM [27].

We conclude that the supersaturated calcium phosphate rinse (Caphosol®) seems to be an effective means to prevent and treat OM in HSCT cancer patients. It requires validation in further trials, before putting it to the everyday use. However, based on available data, this preparation being easy-to-apply, non-toxic and cost-effective already seems that it will become a new hope for a better solution of the old problem of OM.

References

1. Bellm L, Epstein J, Rose-Ped A, Martin P, Fuchs H. Patient reports of complications of bone marrow transplantation. Support Care Cancer 2000; 8: 33-39.
2. Epstein J, Schubert M. Oropharyngeal mucositis in cancer therapy: review of pathogenesis, diagnosis, and management. Oncology 2003; 17: 1767-1779.
3. Pico J, Avila-Garavito A, Naccache P. Mucositis: its occurrence, consequences, and treatment in the oncology setting. The Oncologist 1998; 3: 446-451.
4. Plevova P. Prevention and treatment of chemotherapy-and radiotherapy-induced oral mucositis: a review. Oral Oncol 1999; 35: 453-470.
5. Sonis S, 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.
6. Gabriel D, Shea T, Olajida O, Serody J, Comeau T. The effect of oral mucositis on morbidity and mortality in bone marrow transplant. Semin Oncol 2003; 30: 76-83.
7. Rapoport A, Miller Watelet L, Linder T et al. Analysis of factors that correlate with mucositis in recipients of autologous and allogeneic stem-cell transplants. J Clin Oncol 1999; 17: 2446-2453.
8. Bolwell B, Kalaycio M, Sobecks R et al. A multivariable analysis of factors influencing mucositis after autologous progenitor cell transplantation. Bone Marrow Transplant 2002; 30: 587-591.
9. Robien K, Schubert M, Bruemmer B, Lloid M, Potter J, Ulrich C. Predictors of oral mucositis in patients receiving hematopoietic cell transplants for chronic myelogenous leukaemia. J

Clin Oncol 2004; 22: 1268-1275.
10. Koestler W, Hejna M, Wenzel C, Zielinski C. Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. CA Cancer J Clin 2001; 51: 290-315.
11. Rubenstein E, Peterson D, Schubert M et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004; 100: 2026-2046.
12. Nasilowska-Adamska B, Rzepecki P, Manko J et al. The influence of palifermin (Kepivance) on oral mucositis and acute graft versus host disease in patients with hematological diseases undergoing hematopoietic stem cell transplant. Bone Marrow Transplant 2007; 40: 983-988.
13. Vanclee A, Lutgens L, Oving E et al. Keratinocyte growth factor ameliorates acute graft-versus-host disease in a novel nonmyeloablative haploidentical transplantation model. Bone Marrow Transplant 2005; 36: 907-915.
14. Keefe DM, Schubert MM, Elting LS et al. Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007; 109: 820-831.
15. Papas A, Clark R, Martuscelli G, O'Loughlin K, Johansen E, Miller K. A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. Bone Marrow Transplant 2003; 31: 705-712.
16. Rzepecki P, Sarosiek T, Barzal J et al. Palifermin for prevention of oral mucositis after haematopoietic stem cell transplantation - single centre experience. J BUON 2007; 12: 477-482.
17. Miller A, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-214.
18. Horsley P, Bauer J, Mazkowiack R, Gardner R, Bashford J. Palifermin improves severe mucositis, swallowing problems, nutrition impact symptoms, and length of stay in patients undergoing hematopoietic stem cell transplantation. Support Care Cancer 2007; 15: 105-109.
19. Haas M, Mercedes T, Manyak M. Reduction of Painful Oral Mucositis by Supersaturated Calcium Phosphate Oral Rinse in Head and Neck Cancer Patients Receiving Chemotherapy and Radiation. Int J Radiat Oncol Biol Phys 2008; 72: S406.
20. Blazar B, Weisdorf D, DeFor T et al. Phase 1/2 randomized, placebo-control trial of palifermin to prevent graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). Blood 2006; 108: 3216-3222.
21. Langner S, Staber P, Schub N et al. Palifermin reduces incidence and severity of oral mucositis in allogeneic stem-cell transplant recipients. Bone Marrow Transplant 2008; 42: 275-279.
22. Radtke M, Kolesar J. Palifermin (KepivanceTM) for the treatment of oral mucositis in patients with hematologic malignancies requiring hematopoietic stem cell support. J Oncol Pharm Pract 2005; 11: 121-125.
23. 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.
24. Cowen D, Tardieu C, Schubert M et al. Low energy helium-neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial 1: 16A survey of 30 patients. Photomed Laser Surg 2010; 27: 137-144.
25. Dumontet C, Sonnet A, Bastion Y, Salles G, Espinouse D, Coiffier B. Prevention of high dose L-PAM-induced mucositis by cryotherapy. Bone Marrow Transplant 1994; 14: 492-494.
26. Eduardo F, Bezinelli L, Luiz A, Correa L, Vogel C, Eduardo C. Severity of oral mucositis in patients undergoing hematopoietic cell transplantation and an oral laser phototherapy protocol. Photomed Laser Surg 2009 27: 137-144.
27. Finch P, Rubin J. Keratinocyte growth factor expression and activity in cancer: implications for use in patients with solid tumors. J Natl Cancer Inst 2006; 98: 812-824.