Bone Marrow Transplantation (2013) **48,** 832–836

www.nature.com/bmt

ORIGINAL ARTICLE

The efficacy of selenium in prevention of oral mucositis in patients undergoing hematopoietic SCT: a randomized clinical trial

Z Jahangard-Rafsanjani[1], K Gholami[2], M Hadjibabaie[2], AR Shamshiri[3], K Alimoghadam[4], A Sarayani[5], M Mojtahedzadeh[1], M Ostadali-Dehaghi[6] and A Ghavamzadeh[6]

Oral mucositis (OM) is a complication of high-dose chemotherapy (HDC) followed by hematopoietic SCT (HSCT) with few effective treatments. Selenium has a cytoprotective role via the glutathione peroxidase (Glu.Px) enzyme and prevents chemotherapy-induced toxicities. We performed a double-blind, randomized, placebo-controlled study to evaluate the efficacy of selenium on the prevention of OM in 77 patients with leukemia, undergoing allogeneic HSCT. Thirty-seven patients received oral selenium tablets (200 mcg twice daily) from the starting day of HDC to 14 days after transplantation. OM was evaluated daily for 21 days after transplantation according to World Health Organization oral toxicity scale. The incidence of severe OM (grades 3–4) was significantly lower in the selenium group (10.8% vs 35.1%, $P<0.05$). We noted that the duration of objective OM (grades 2–4), excluding patient's self-declaration (grade 1), was significantly shorter in the selenium group (3.6 ± 1.84 vs 5.3 ± 2.2 days, $P=0.014$). Significant elevations in serum selenium level and plasma Glu.Px activity were observed 7 and 14 days after transplantation compared with baseline in the selenium group. We conclude that selenium can reduce the duration and severity of OM after HDC. Clinicaltrial.org ID: *NCT01432873*.

Bone Marrow Transplantation (2013) **48,** 832–836; doi:10.1038/bmt.2012.250; published online 7 January 2013

Keywords: selenium; oral mucositis; hematopoietic SCT; antioxidant; randomized controlled trial

INTRODUCTION

High-dose chemotherapy (HDC) followed by hematopoietic SCT (HSCT) is an effective treatment for hematologic malignancies. Oral mucositis (OM), the consequence of injury to the epithelial cells of oral cavity, is a frequent complication of such an aggressive chemotherapy regimen, as patients receiving HDC have an approximately 76% risk of developing this complication.[1] OM usually manifests as diffuse, painful ulcerative lesions, which typically occurs within 2 weeks after the HDC regimen. Serious consequences of OM include pain, increased risk of infection, impaired nutritional intake and prolonged hospitalization. Despite the use of a variety of agents for OM prevention, it still remains as a major complication in post HDC care.[2]

OM appears to be the result of sequential biological events that begin in the submucosa and progress to the epithelium. This process can be divided into five phases: initiation, message generation, signaling and amplification, ulceration and finally healing. It seems that generation of oxidative stress and reactive oxygen species is the origin of injuries to the mucosal cells.[3] On the other hand, production of pro-inflammatory cytokines including TNF-α, and the ILs (IL-1, IL2 and IL-6) seems to have a role in development of OM.[1,4] Hence, mechanistically, antioxidant and anti-inflammatory agents could be effective in prevention of this side effect. Several studies have shown that these agents have some benefits in prevention of OM induced by both chemotherapy and radiation therapy.[3,5–8]

Selenium, an essential trace element, acts as both an antioxidant and anti-inflammatory agent. It is involved in several key metabolic activities through selenoproteins, which are essential for protection against oxidative damage.[9] In other words, selenium is a cofactor for glutathione peroxidase (Glu.Px), an endogenous enzyme system, which is able to scavenge free radicals.[10] In this context, some animal studies have shown that adequate supplementation of selenium could produce cytoprotective effects and anti-ulcer activity.[11,12] A pilot investigation has shown a lower incidence and grade of OM in patients receiving selenium selinate during radiochemotherapy for treatment of head and neck cancer.[13] Moreover, it has been reported that selenium administration could be useful in amelioration of some side effects of chemotherapy other than mucositis.[14] For instance, inflammation, oxidative stress injury and apoptosis probably have the main roles in development of the nephrotoxicity induced by cisplatin.[15] Some human and animal studies have shown that co-administration of selenium with cisplatin could decrease the renal injury.[15–17]

We have formerly shown that selenium deficiency exists in almost all the patients undergoing HSCT in our institution.[18] Therefore, we decided to evaluate the efficacy of selenium intake for prevention of OM in patients with hematologic malignancies candidate for allogeneic HSCT after receiving HDC. To the best of our knowledge, this is the first investigation regarding the use of selenium administration in this setting.

[1]Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; [2]Faculty of Pharmacy, and Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran; [3]Dental Research Center, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran; [4]Hematology-Oncology Department, Hematology-Oncology and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran; [5]Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran and [6]Hematology-Oncology, and Stem Cell Transplantation Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. Correspondence: Dr M Hadjibabaie, Clinical Pharmacy Department, Faculty of Pharmacy, and Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, 4th Floor, No. 92, Karimkhan Zand Avenue, Hafte Tir Square, Tehran 1417614411, Iran.
E-mail: mhadjibabaie@yahoo.com
Received 11 September 2012; revised 28 October 2012; accepted 6 November 2012; published online 7 January 2013

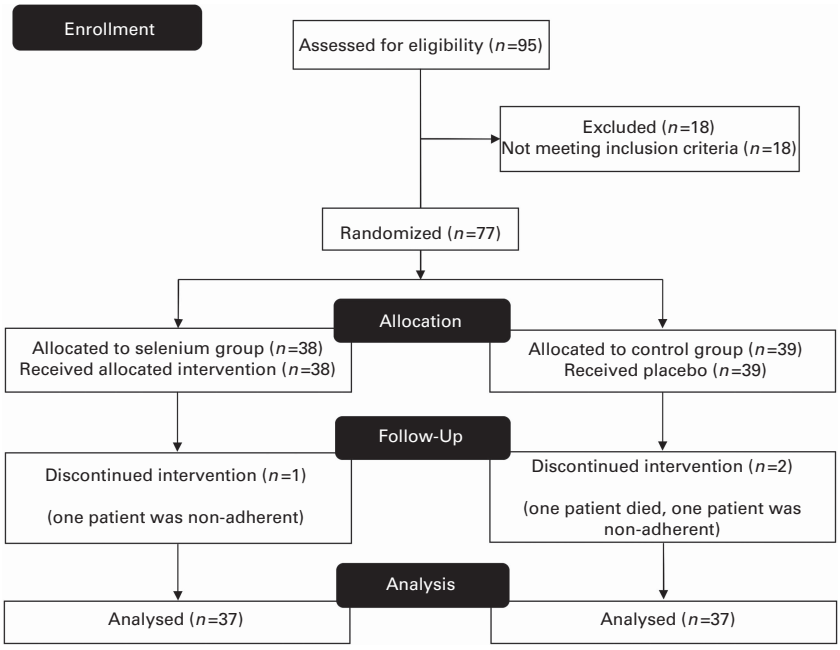

Figure 1. Study participants flow diagram.

PATIENTS AND METHODS

We performed a double-blind, randomized, placebo-controlled study from June 2011 to July 2012 in the Hematology–Oncology and Stem Cell Transplantation Research Center (Shariati Hospital), Tehran University of Medical Sciences, Tehran, Iran. The institutional review board approved the study protocol and written informed consent was obtained from each subject before any study-related procedure.

Patients

Adult patients with AML or ALL, undergoing allogenic HSCT, were enrolled in the study. All patients had adequate cardiac, pulmonary, renal and hepatic function, as determined by the institutional protocol. Subjects were excluded from the study if they had a Karnofsky performance status $<70\%$. The study sample size ($n=76$, 38 participants in each study group) was calculated assuming a 30% decrease in the incidence of OM,[7] a statistical power 80%, and a two-sided significance level of 5%.

Intervention

Patients were randomly allocated to selenium or control group in a blocked randomization schedule. We administered either selenium tablet (Webber Naturals, Coquitlam, BC, Canada, 200 mcg) or placebo tablet twice daily, from the starting day of HDC to 14 days after transplantation. Chemotherapy regimen and supportive care were administered according to the standard institutional practice. The HDC included BU 4 mg/kg p.o. in divided doses daily for 4 days (total dose 16 mg/kg) followed by CY 60 mg/kg once daily i.v. for 2 days (total dose 120 mg/kg). Patients received peripheral blood hematopoietic stem cells 1 day after completion of chemotherapy. All the patients received a similar regimen for prevention of mucositis, which included 20 drops of nystatin every 3 h, a chewable tablet of sucralfate 500 mg every 8 h and mouth washes containing 10 cc chlorhexidine 0.02% plus 10 cc diluted povidone iodine every 3 h. Narcotic analgesics were rarely used to alleviate OM in our institution.

Study outcomes

Assessment of OM. Grade of OM was the primary outcome in our study, which was evaluated with the use of five-grade World Health Organization (WHO) oral toxicity scale.[19] The WHO oral toxicity scale combines the clinician-based observations with the impact of mucositis on patient's ability to eat.[20] Severity of OM is graded from no mucositis (grade 0) to severe mucositis in which alimentation is not possible (grade 4).

Assessment of OM was carried out by one author (ZJ-R) under supervision of the attending physician (KA). The outcome assessor and the attending physician were blinded to patients' allocation. Each patient was assessed for OM on a daily basis (except on weekends and holidays) from the starting day of HDC to 21 days after transplantation or until OM was resolved. We determined the incidence, severity and duration of OM.

Assessment of other indices. Several hematological indices were assessed including the duration of ANC under 500 cells/mm^3, neutrophil and platelet engraftment time (the time point after transplantation at which a patient can maintain a sustained ANC of >500 cells/mm^3 and a sustained platelet count of at least 20 000/mm^3 lasting 3 consecutive days without transfusions during hospital stay). Moreover, the amount of red cell and platelet transfusion were evaluated.

Non-hematological indices, such as serum creatinine level and blood urea nitrogen test for renal function assessment and aspartate aminotransferase and alanine transaminase for liver function assessment, were recorded daily, from first day of admission until discharge.

Additional exploratory end points included duration of fever, length of hospital stay and incidence of acute GVHD and mortality rate at 3 months follow-up.

Laboratory procedures

Serum selenium level and Glu.Px activity were determined before and during selenium administration. Accordingly, blood samples were collected in three phases: before starting HDC, 7 days and 14 days after transplantation.

To assay serum selenium level, blood samples (4 mL) were collected in serum-separating tubes and centrifuged for 10 min and the serum was removed and stored at $-70\,^{\circ}$C until the assay. The selenium level was determined by the graphite furnace atomic absorption spectrometry (SpectrAA 220, GTA 110, Varian, Australia). For assaying Glu.Px activity, blood samples (1 mL) were collected in citrated tubes and centrifuged for 10 min. The plasma was removed and stored at $-70\,^{\circ}$C until the assay. The Glu.Px activity was measured by using Cayman's Glu.Px assay kit (Ann Arbor, MI, USA) (item no. 703102), based on the calorimetric method used by Paglia and Valentine.[21]

Statistical analysis

Continuous variables were reported as mean $\pm$ s.d. and categorical data as percentage. For comparing continuous and categorical data between study groups, independent samples *t*-test and χ^2 (or Fisher's exact test if appropriate) were performed, respectively. *P*-values <0.05 was considered as statistically significant and *P*-values between 0.05 and 0.08 was accepted as marginally significant.

Table 1. Baseline characteristics of the patients

Characteristic	*Selenium group (N = 37)*	*Control group (N = 37)*
Male sex, *n* (%)	21 (56.8%)	21 (56.8%)
Age, year		
Mean	33.3	34.0
Median	32	32
Range	18–55	18–55
Disease type, n (%)		
AML	23 (62.2)	23 (62.2)
ALL	14 (37.8)	14 (37.8)
Disease status before transplantation, n (%)		
CR_1	26 (70.3)	28 (77.8)
CR_2	9 (24.3)	7 (19.4)
CR_3	2 (5.4)	1 (2.8)

Abbreviation: CR = Complete remission.

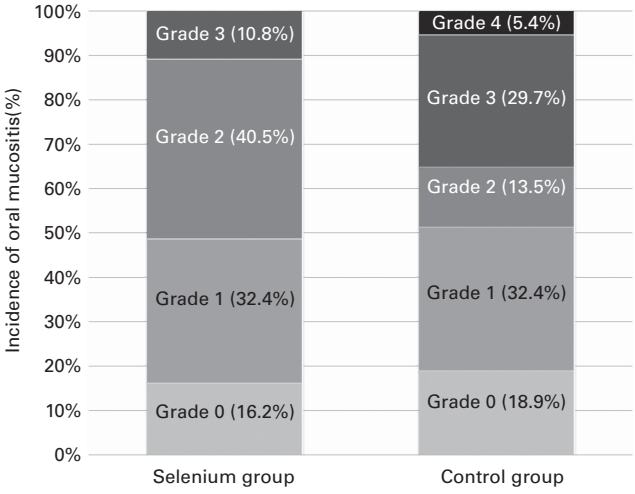

Figure 2. Incidence of OM in the selenium and control groups.

RESULTS

Seventy-seven patients participated in the study. Of these, 74 patients completed and 3 patients discontinued the study (Figure 1). The baseline characteristics of the patients were similar in the study groups (Table 1). Narcotic analgesics were used concurrently during OM presentation in five patients (three patients in the selenium group vs two patients in the control group, $P = 0.64$).

The cumulative incidence of OM (WHO scale grades of 1–4) in the selenium group and control group was not significantly different (83.8% vs 81.1%, $P = 0.76$). On the contrary, the incidence of severe OM (grades 3 and 4) was significantly lower in the selenium group (10.8% vs 35.1%, $P = 0.013$; Figure 2). Two patients in the control group experienced WHO OM grade 4 whereas none of the patients in the selenium group developed this grade of OM. The mean duration of OM was not different between two groups ($P = 0.48$); however, we interestingly noted that the mean duration of OM from the beginning of grade 2, moving up to grade 4 and then returning to grade 2 was significantly lower in the selenium group ($P = 0.014$). There was no difference in the start day of OM between two groups. The effect of selenium on OM is summarized in Table 2.

All patients in this study had successful engraftment. No difference was observed between two groups regarding the neutrophil and platelet engraftment time (Table 3). Nevertheless, the mean duration of neutropenia was 8.38 ± 2.6 days in the selenium group and 9.35 ± 1.98 days in the control group (marginally significant, $P = 0.076$). RBC and platelet transfusion requirements did not differ between two groups ($P = 0.95$ and 0.67, respectively).

Fever above 38.3 °C was observed in 72 patients (97.3%) during neutropenic phase. Fever duration was similar in two groups (3.81 ± 1.96 days in selenium group and 3.83 ± 2.93 days in control group, $P = 0.98$). Length of hospital stay did not differ between the two groups (26.92 ± 6.26 days in selenium group and 25.81 ± 4.33 days in control group, $P = 0.38$).

No significant differences were observed between two groups in other transplant-related end points, such as the incidence of acute GVHD or its severity, renal or hepatic function during hospitalization and mortality rate 3 months after transplantation (Table 4).

The data on serum selenium level and plasma Glu.Px activity are shown in Table 5. In the selenium group, significant elevations in serum selenium level and plasma Glu.Px activity in comparison with baseline were observed 7 days ($P = 0.02$ and $P = 0.001$, respectively) and 14 days (both P values = 0.0001) after transplantation. There was a significant difference in mean serum selenium level between two groups at 14 days after transplantation (8.34 mcg/dL in the selenium group vs 7.36 mcg/dL in the control group, $P = 0.018$). Moreover, plasma Glu.Px activity was significantly higher in the selenium group at the same time point (118.21 vs 94.78 nmol/min/mL, $P = 0.008$).

Table 2. Effect of selenium on oral mucositis

Variables	*Selenium group (N = 37)*	*Control group (N = 37)*	P-*value*
Oral mucositis incidence	31 (83.8)[a]	30 (81.1)	0.76
Incidence of grades 1–2	27 (73)	17 (46)	0.01
Incidence of grades 3–4	4 (10.8)	13 (35.1)	
Duration of oral mucositis (days)	7.06 ± 2.51[b]	7.56 ± 3.01	0.48
Duration of grades 2–4 oral mucositis (days)	3.6 ± 1.84	5.3 ± 2.2	0.01
The start day of oral mucositis after HSCT	6.16 ± 1.57	6.27 ± 1.8	0.81

Abbreviation: HSCT = hematopoietic SCT. [a]Number in parenthesis is reported as percentage. [b]Values are shown as mean ± s.d.

Table 3. Neutrophil and platelet engraftment

Variables	*Selenium group (N = 37)*	*Control group (N = 37)*	P-*value*
Duration of neutropenia[a]	8.38 ± 2.62[b]	9.35 ± 1.99	0.076
Neutrophil engraftment time[c]	13.11 ± 2.62	13.70 ± 2.46	0.32
Platelet engraftment time[d]	12.54 ± 2.53	12.67 ± 4.29	0.87
Transfusion requirements			
No. of packed cell transfusions	1.03 ± 1.72	1.05 ± 1.67	0.95
No. of platelet unit transfusions	1.32 ± 2.19	1.14 ± 1.49	0.67

[a]Duration of neutrophil count < 500 cells/mm^3 in days. [b]All numbers reported in mean ± s.d. [c]Neutrophil count > 500 cells/mm^3—days after transplant. [d]Platelet count $> 20\,000$/mm^3—days after transplant.

Table 4. Transplant-related end points

Variables	*Selenium group (N = 37)*	*Control group (N = 37)*	P-*value*
Incidence of acute GVHD during hospitalization	14 (37.8%)[a]	19 (51.4%)	0.35
Incidence of serum creatinine elevation	3 (8.1%)	7 (18.9%)	0.31
Incidence of ALT or AST elevation	11 (29.7%)	13 (35.1%)	0.62
Mortality rate in 3 months after transplantation	3 (8.1%)	4 (10.8%)	0.69

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase. [a]Number in parentheses are reported as percentage.

Table 5. Serum selenium concentration and plasma glutathione peroxidase activity

Variables	*Selenium group (N = 37)*	*Control group (N = 37)*	P-*value*
Selenium level (mcg/dL)			
Baseline	6.47 ± 1.53	7.13 ± 1.70	0.08
7 days after transplantation	7.16 ± 1.41	7.15 ± 1.48	0.98
14 days after transplantation	8.34 ± 1.60	7.36 ± 1.84	0.018
Glutathione peroxidase activity (nmol/min/mL)			
Baseline	86.75 ± 28.69	83.62 ± 25.16	0.62
7 days after transplantation	102.09 ± 31.66	97.87 ± 25.61	0.53
14 days after transplantation	118.21 ± 41.50	94.78 ± 27.07	0.008

DISCUSSION

Different strategies have been used to prevent OM. Although only two interventions, keratinocyte growth factor (palifermin) and cryotherapy, have revealed some advantages in preventing OM.[22,23] Other agents such as aloe vera, cytoprotective agents (amifostine), i.v. glutamine, G-CSF, honey and laser have also showed weaker evidence of benefit.[2] Palifermin is the only Food and Drug Administration approved drug for prevention of mucositis in patients with hematologic malignancies who receive high doses of chemotherapy and radiation therapy followed by HSCT.[24] However, Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology guidelines recommend its use only for patients undergoing autologous HSCT.[25]

The result of our study determined that selenium can significantly reduce the incidence of severe OM (grades 3–4) after HDC in allogeneic HSCT. As formerly mentioned, selenium is a cofactor for Glu.Px, an endogenous enzyme system, which functions as a free radical scavenger.[10] Previously, Thieblemont *et al.*[7] evaluated another cytoprotective agent, amifostine, in patients with multiple myeloma undergoing autologous HSCT. Their results also showed a reduction of mucosal damage after high-dose melphalan conditioning regimen.

Another positive finding of our study was a marginally significant reduction in neutropenia duration in the selenium group. Few clinical trials have investigated the effect of selenium supplementation during cancer chemotherapy.[17,26] However, in accordance with our finding, these studies demonstrated significant reduction of neutropenia induced by chemotherapy agents without any loss of chemotherapeutic efficacy in association with selenium supplementation. Other hematological indices such as neutrophil and platelet engraftment time were similar in both treatment arms in the present study. Our findings are in line with Thieblemont *et al.*[7] study of amifostine in HSCT patients.

Despite positive findings about mucositis severity and its duration, there were no significant differences in the incidence of fever and length of hospital stay between the two groups in our study. These findings are similar to Thieblemont *et al.*[7] study and Nasilowska *et al.*[27] trial that administered amifostine and palifermin, respectively, to reduce OM in HSCT setting. In contrast, significant reduction in the length of hospital stay of patients treated with palifermin has also been reported.[28] We also observed no significant differences between two groups in other transplant-related end points, such as the incidence or severity of acute GVHD and renal or hepatic function during hospitalization. This might be due to lack of sufficient statistical power and must be addressed in future larger trials.

Significant increases in serum selenium levels and plasma Glu.Px activity in the selenium group, confirmed that improvement of the patients' selenium status was achievable during development of oral injury. Nevertheless, it has been previously determined that Glu.Px activity is optimum when serum selenium levels exceed 9.5 mcg/dL.[29,30] In our study, the mean plasma selenium concentration was found to be 8.34 mcg/dL after 21 days of selenium administration. Hence, it could be hypothesized that earlier administration of selenium would result in optimum serum levels.

To our knowledge, there are no other controlled trials to measure the efficacy of selenium for the prevention of OM in patients undergoing HSCT. Therefore, the selenium administration protocol in our study may require further justification. We used the upper human safe limit dose of oral selenium (400 mcg)[31] as an optimal dose of selenium supplementation has not been determined in HSCT literature. We started the administration of selenium from the starting day of HDC. This protocol was designed on the basis of following rationales: (1) elevation of serum selenium level within 2 weeks after initiation of selenium supplementation[32] and (2) development of HDC-induced mucosal injury within 1 week of chemotherapy administration and reaching its highest severity within 2 weeks.[3]

Strength and limitations

We used a double-blind, randomized, controlled study design to maximize the internal validity of our results. Outcome assessment was carried out by one clinician, which eliminated the risk of inter-rater variability. We used oral selenium supplementation in our study, which might be affected by patients' low compliance. Nevertheless, we did not observe any evidence of noncompliance.

CONCLUSION

In summary, the results of our study showed that selenium supplementation during HDC could prevent severe OM in patients undergoing allogeneic HSCT. As this study was the first experience of selenium administration in HSCT setting, further randomized controlled trials should be designed to investigate the optimal dose, appropriate duration of administration and long-term post transplant outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We express our gratitude to the staff of BMT wards 1 and 2, especially Mrs Mousavi and Mrs Shahriari, at the Hematology-Oncology and Stem Cell Transplantation Research Center, Shariati Hospital.

REFERENCES

1 D'Hondt LLC, Marc A, Jean-Luc C. Oral mucosit is induced by anticancer treatments: physiopathology and treatments. *Ther Clin Risk Manag* 2006; **2**: 159–168.
2 Worthington HV, Clarkson JE, Eden O. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2011; **4**: CD000978.
3 Sonis ST. A biological approach to mucositis. *J Support Oncol* 2004; **2**: 21–32.
4 Lalla RV, Schubert MM, Bensadoun RJ, Keefe D. Anti-inflammatory agents in the management of alimentary mucositis. *Support Care Cancer* 2006; **14**: 558–565.
5 Porta C, Moroni M, Nastasi G. Allopurinol mouthwashes in the treatment of 5-fluorouracil-induced stomatitis. *Am J Clin Oncol* 1994; **17**: 246–247.
6 Epstein JB, Silverman Jr S, Paggiarino DA, Crockett S, Schubert MM, Senzer NN *et al.* Benzydamine HCl for prophylaxis of radiation-induced oral mucositis. *Cancer* 2001; **92**: 875–885.
7 Thieblemont C, Dumontet C, Saad H, Roch N, Bouafia F, Arnaud P *et al.* Amifostine reduces mucosal damage after high-dose melphalan conditioning and autologous peripheral blood progenitor cell transplantation for patients with multiple myeloma. *Bone Marrow Transplant* 2002; **30**: 769–775.
8 Ertekin MV, Koē M, Karslioglu I, Sezen O. Zinc sulfate in the prevention of radiation-induced oropharyngeal mucositis: a prospective, placebo-controlled, randomized study. *Int J Radiat Oncol Biol Phys* 2004; **58**: 167–174.
9 Ryan-Harshman M, Aldoori W. The relevance of selenium to immunity, cancer, and infectious/inflammatory diseases. *Can J Diet Pract Res* 2005; **66**: 98–102.
10 Buntzel J, Micke O, Mucke R, Glatzel M. Amifostine and selenium during simultaneous radiochemotherapy in head and neck cancer - redox status data. *Trace Elem Electrolytes* 2005; **22**: 211–215.
11 Al-Moutairy AR, Tariq M. Effect of vitamin E and selenium on hypothermic restraint stress and chemically-induced ulcers. *Dig Dis Sci* 1996; **41**: 1165–1171.
12 Koyuturk M, Bolkent S, Ozdil S, Arbak S, Yanardag R. The protective effect of vitamin C, vitamin E and selenium combination therapy on ethanol-induced duodenal mucosal injury. *Hum Exp Toxicol* 2004; **23**: 391–398.
13 Buntzel J, Glatzel M, Kisters K, Mucke R, Bruns F, Schonekaes K *et al.* Selenium as radioprotector in head and neck cancer patients-First clinical results. *Trace Elem Electrolytes* 2006; **23**: 178–180.
14 Fakih M, Cao S, Durrani FA, Rustum YM. Selenium protects against toxicity induced by anticancer drugs and augments antitumor activity: a highly selective, new, and novel approach for the treatment of solid tumors. *Clin Colorectal Cancer* 2005; **5**: 132–135.
15 Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. *Am J Med Sci* 2007; **334**: 115–124.
16 Camargo SMR, Francescato HDC, Lavrador MAS, Bianchi MLP. Oral administration of sodium selenite minimizes cisplatin toxicity on proximal tubules of rats. *Biol Trace Elem Res* 2001; **83**: 251–262.
17 Hu YJ, Chen Y, Zhang YQ, Zhou MZ, Song XM, Zhang BZ *et al.* The protective role of selenium on the toxicity of cisplatin-contained chemotherapy regimen in cancer patients. *Biol Trace Elem Res* 1997; **56**: 331–341.
18 Hadjibabaie M, Iravani M, Shamshiri AR, Zaker Z, Mousavi A, Alimoghaddam K *et al.* The prevalence of low selenium levels in adult patients undergoing bone marrow transplantation: a brief communication. *Nutr Cancer* 2008; **60**: 837–839.
19 Mansouri A, Hadjibabaie M, Iravani M, Shamshiri AR, Hayatshahi A, Javadi MR *et al.* The effect of zinc sulfate in the prevention of high-dose chemotherapy-induced mucositis: a double-blind, randomized, placebo-controlled study. *Hematol Oncol* 2012; **30**: 22–26.
20 Sonis ST. Oral mucositis. *Anticancer Drugs* 2011; **22**: 607–612.
21 Paglia DE, Valentine WN. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. *J Lab Clin Med* 1967; **70**: 158–169.
22 Lilleby K, Garcia P, Gooley T, McDonnnell P, Taber R, Holmberg L *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.
23 Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T *et al.* Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med* 2004; **351**: 2590–2598.
24 Keefe D, Lees J, Horvath N. Palifermin for oral mucositis in the high-dose chemotherapy and stem cell transplant setting: the Royal Adelaide Hospital Cancer Centre experience. *Support Care Cancer* 2006; **14**: 580–582.
25 Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE *et al.* Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; **109**: 820–831.
26 Sieja K, Talerczyk M. Selenium as an element in the treatment of ovarian cancer in women receiving chemotherapy. *Gynecol Oncol* 2004; **93**: 320–327.
27 Nasilowska-Adamska B, Rzepecki P, Manko J, Czyz A, Markiewicz M, Federowicz I *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.
28 Horsley P, Bauer JD, 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.
29 Muecke R, Schomburg L, Glatzel M, Berndt-Skorka R, Baaske D, Reichl B *et al.* Multicenter, phase 3 trial comparing selenium supplementation with observation in gynecologic radiation oncology. *Int J Radiat Oncol Biol Phys* 2010; **78**: 828–835.
30 Lymbury R, Tinggi U, Griffiths L, Rosenfeldt F, Perkins AV. Selenium status of the Australian population: effect of age, gender and cardiovascular disease. *Biol Trace Elem Res* 2008; **126**: 1–10.
31 Hurst R, Armah CN, Dainty JR, Hart DJ, Teucher B, Goldson AJ *et al.* Establishing optimal selenium status: results of a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* 2010; **91**: 923–931.
32 Reid ME, Stratton MS, Lillico AJ, Fakih M, Natarajan R, Clark LC *et al.* A report of high-dose selenium supplementation: response and toxicities. *J Trace Elem Med Biol* 2004; **18**: 69–74.