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A comparison of dioctahedral smectite and iodine glycerin cream with topical mouth rinse in treatment of chemotherapy induced oral mucositis: A pilot study

Jin-Xiang Lin [a, 1], Zu-Yan Fan [a, 1], Qu Lin [a, 1], Dong-Hao Wu [a, 1], Xiang-Yuan Wu [a, 1], Yan-Ru Chen [a], Heng-Ying Fang [a], Dong-Bing Wu [b], Jing-Yun Wen [a], Min Dong [a], Xiao-Kun Ma [a], Xiang-Bo Wan [c, *]

[a] Department of Medical Oncology, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China
[b] Department of Hematology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China
[c] Gastrointestinal Institute, the Sixth Affiliated Hospital of Sun Yat-sen University, 26# YuanCun ErHeng Road, Guangzhou 510655, China

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A B S T R A C T

Purpose of the research: To compare the efficacy of dioctahedral smectite and iodine glycerin (DSIG) cream with topical mouth rinse (composed of saline, gentamicin and Vitamin B_{12}) in treatment of chemotherapy induced oral mucositis (OM).

Methods and sample: A total of 130 intensive chemotherapy or stem cells transplantation induced OM patients were recruited. Among these patients, 67 patients received topical mouth rinse and 63 patients received DSIG cream treatment. The OM would be treated on the OM appearance and sustained for 5 days. OM severity was measured daily using The American Oncology Nursing Society recommended Oral Assessment Guideline (OAG) score system.

Key results: Compared with topical mouth rinse treatment, a significant lower OAG score was observed in DSIG cream treated patients. Specifically, the OAG scores were respectively 12.1 ± 1.1, 12.0 ± 1.2, 11.3 ± 1.3 and 10.4 ± 1.3 from day 2 to day 5 in topical mouth rinse treatment subgroup. Correspondingly, the OAG scores were respectively 10.2 ± 1.0, 9.3 ± 0.9, 8.5 ± 0.6 and 8.0 ± 0.2 for DSIG cream treatment subset (all $P < 0.05$). Importantly, compared with topical mouth rinse treatment, the DSIG cream significantly shortened OM repair time (4.68 ± 0.98 vs. 8.76 ± 1.80 days, $P < 0.001$). After 5 days treatment, 54 patients (85.7%) obtained complete regression with an OAG score ≤ 8, and 7 patients (11.1%) had partial regression with an OAG score of 9–10 in DSIG cream treatment subgroup. However, only 2 patients (3.0%) obtained completed regression and 32 patients (47.8%) had partial regression in topical mouth rinse treatment cohort. Moreover, no serious side-effect was observed in both cohorts.

Conclusions: Compared with topical mouth rinse, DSIG cream significantly lowered the OAG score and shortened OM duration.

Introduction

Oral mucositis (OM), presenting as painful ulcerative and inflammatory disease in oral mucosa, is a common side effect during cancer treatment, such as hematopoietic stem cell transplantation and chemoradiotherapy (Vera-Llonch et al., 2007). Under physiological conditions, oral mucosa and normal saliva activity are two important barriers to prevent microorganism invasion (Geckili et al., 2012). Moreover, the high mitotic rate made the oral epithelia with rapid proliferation to repair the impaired mucosa (Wu et al., 2012). However, due to the direct toxic effect of cytoxic agents, including 5-Fluorouracil (5-FU), Methotrexate, Doxorubicin, Etoposide and Vinblastine, the normal physiological self-repair function in oral mucosa will be disturbed (Bensinger et al., 2008; Naidu et al., 2004; Ohbayashi et al., 2008; Svanberg et al., 2010). Indeed, the incidence of OM was ranged from 15% to 40% in patients receiving cytotoxic chemotherapy, and was from 70% to 90% in patients given bone marrow transplantation (Ohbayashi et al., 2008; Vokurka et al., 2011). In a multicenter study, the chemotherapy induced OM was reported to impair of the functions of eating (82.4%), swallowing (78.9%), drinking (75.4%), sleeping (71.9%) and talking (43.9%) (Cheng et al., 2012). Significantly, 39.0%

* Corresponding author. Tel.: +86 20 38379683; fax: +86 20 38254221.
E-mail address: wanxbo@mail.sysu.edu.cn (X.-B. Wan).
[1] These authors contributed equally to this work.

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of patients had at least two simultaneous symptoms, and 24.6% of patients had all five symptoms concurrently (Cheng et al., 2012). Moreover, OM might cause profound psychological distress and impair quality of life (Cheng et al., 2012; Kim et al., 2012). In particular conditions, the chemotherapy intensity will be reduced due to OM caused side effects, and subsequently compromise the efficacy of the cytotoxic agents (Naidu et al., 2004). Therefore, it is necessary to develop more clinical adaptable approaches to manage the chemotherapy induced OM.

A series of pharmacological and nonpharmacological approaches have been developed for decades to treat chemotherapy and or radiotherapy-induced OM. However, none of these methods proved to be completely effective to date (Worthington et al., 2011). In a recent phase III, randomized, double-blind trial, doxepin rinse significantly decreased the mouth and throat pain than placebo for radiochemotherapy induced OM. However, 17% of patients were discontinued the rinses due to the adverse effects of burning discomfort and increased drowsiness (Leenstra et al., 2014). Moreover, cryotherapy and laser therapy had been used to treat OM for decades. In a prospective clinical study, compared with laser therapy (InGaAlP, 660 nm, 40 mW, 6 J/cm^2) alone, cryotherapy (ice chips) plus laser therapy lowered the OM severity and reduced the OM duration for patients received hematopoietic stem-cell transplantation (de Paula Eduardo et al., 2014). Despite the favorable efficacy, the cryotherapy had been found to be discomfortable during the therapy with ice, such as chills and nausea (Aisa et al., 2005; Mori et al., 2006). Thus, more effective approaches that have less side effects should be eagerly pursued to anticancer therapy induced OM.

Dioctahedral smectite (DS), the natural adsorbent clay formed of sheet of aluminomagnesium silicate, is efficient to protect gastrointestinal mucosa (Mujawar et al., 2012). This natural clay functions to reduce microbe, enhances the intestinal barrier and prevents the mucosal damage (Liu et al., 2012). Moreover, the disruption of the intestinal barrier may be exacerbated by the release of pro-inflammatory cytokines TNF, and by the bacterial colonization (Logan et al., 2008; Ong et al., 2010). Non-antibiotic topical antiseptics, including of iodine solutions (Cooper, 2007), gentian violet (Vazquez, 1999) and silver coordination polymers (Gordon et al., 2010), are effective in treating mucosal ulcers and have strong antimicrobial efficacy. On metallic implant substrates, silver coordination polymers exhibited strong biofilm sugar-independent bactericidal activity and prevented murine Staphylococcus epidermidis implant infection (Gordon et al., 2010). In an in vivo study, treatment with povidone–iodine or chlorhexidine yielded at least a 4-log reduction in bacterial intensity for gastrointestine mucosa (Ryou et al., 2012). Importantly, oral cavity epithelial and gastrointestinal mucosas have the similar physiological property and pathological reaction to chemotherapy (Lalla et al., 2014a). Thus, the reagent that was effective to prevent gastrointestinal mucositis might be also useful to OM. However, the mixture of DS and non-antibiotic topical antiseptics in treating OM had not yet been tested.

In the present study, we compared the efficacy of dioctahedral smectite and iodine glycerin (DSIG) cream and topical mouth rinse to chemotherapy induced OM. The purposes of this paper were to evaluate the feasibility of DSIG cream to reduce the OM related symptoms, and test its potential in future clinical implication.

Patients and methods

Patients

Eligible inpatients were those with age 18 years or older, pathological confirmed malignant tumors or malignant hematological diseases, performance status score of 0–2, and had chemotherapy induced OM. From January 2009 to December 2009, 138 OM patients that received 5-Fluorouracil (5-FU), Methotrexate, Doxorubicin, Etoposide or Vinblastine contained chemotherapy were recruited at the Third Affiliated Hospital and Sun Yat-sen Memorial Hospital of Sun Yat-sen University. The chemotherapeutic regimens and treatment intensity were administrated as National Comprehensive Cancer Network (NCCN) clinical practice guideline recommended. As shown in Table 1, the chemotherapy protocol included R-CHOP for lymphoma, AC-T and EC-T for breast cancer, and FOLFIRI and MFOLFOX6 for colorectal cancer. Patients were excluded from this study with the following exclusion criteria: gingival ulcers, apicitis, oral cavity infection, malignant tumor of oral cavity, allergy to iodine and Eastern Cooperative Oncology Group Performance Status score greater than 2. The informed consent was obtained prior to chemotherapy, and the study was approved by the Clinical Ethics Review Committee in the Third Affiliated Hospital, Sun Yat-sen University.

OM evaluation

The severity of OM was evaluated by The American Oncology Nursing Society recommended Oral Assessment Guide (OAG) (Eilers et al., 1988). Briefly, the OAG consists of eight oral related functions or features, including of voice, ability to swallow, lips, saliva, tongue, mucous membrane, gingival and teeth. Based on the severity of each function or feature, each component of the score can be given a score between 1 and 3 with score of 3 is the worst. Eight components of scores were added to get an overall score. Therefore, the highest OAG score would be 24. Moreover, OAG score less than 8 was regarded as normal, and OAG score greater than or equal to 8 was viewed as OM.

Table 1
Patient characteristics.

Characteristics	No. patients (%)	Topical mouth rinse ($n = 67$)	DSIG mixture ($n = 63$)	*P* value
Age (yrs)				
<53	61 (46.9)	30	31	0.61
≥53	69 (53.1)	37	32	
Gender				
Male	94 (72.3)	49	45	0.83
Female	36 (27.7)	18	18	
Tumor types				
Lymphoma	48 (36.9)	24	24	0.96
Breast cancer	44 (33.9)	23	21	
Colorectal cancer	38 (29.2)	20	18	
Chemotherapy regimen				
R-CHOP	48 (36.9)	24	24	0.98
AC-T	30 (23.1)	15	15	
EC-T	14 (10.8)	8	6	
FOLFIRI	14 (10.8)	7	7	
mFOLFOX6	24 (18.4)	13	11	
Chemotherapy cycle				
R-CHOP (3 W/C × 6)	48 (36.9)	24	24	0.98
AC (3 W/C × 4)–T (3 W/C × 4)	30 (23.1)	15	15	
EC (3 W/C × 4)–T (3 W/C × 4)	14 (10.7)	8	6	
FOLFIRI (2 W/C × 12)	14 (10.7)	7	7	
mFOLFOX6 (2 W/C × 12)	24 (18.5)	13	11	
OAG score				
8–10	109 (83.8)	57	52	0.52
11–12	20 (15.4)	9	11	
≥13	1 (0.08)	1	0	
ECOG PS				
0–1	128 (98.5)	66	62	0.97
2	2 (1.5)	1	1	

OM, oral mucositis; OAG, Oral Assessment Guideline; ECOG PS, Eastern Cooperative Oncology Group Performance Status; W/C, week/cycle.