

## RESEARCH ARTICLE

# Safety and Efficacy of a Mouth-Rinse with Granulocyte Colony Stimulating Factor in Patients with Chemotherapy-Induced Oral Mucositis

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## Abstract

**Objective:** To assess the safety and effectiveness of a mouth-rinse with G-CSF (JiSaiXin, produced by NCPC Biotechnology Co., Ltd) in treating patients with chemotherapy-induced oral mucositis (CIM). **Method:** A consecutive cohort of patients with advanced cancers and CIM were treated with mouth-rinse G-CSF. All chemotherapy for patients with advanced cancers was adopted from regimens suggested by NCCN guidelines. The mouth-rinse with G-CSF at a dose of 150-300ug plus 100ml-500ml normal saline was started from the time of oral mucositis was confirmed and continuously used for at least 7 days as one course. After at least two courses of treatment, safety and efficacy were evaluated. **Results:** There were 7 female and 7 male patients with advanced cancer and CIM recruited into this study, including 5 with colorectal, 2 with lung, 1 patient with gastric, 1 with cervical and 1 with pancreatic cancer, as well as 2 patients with diffuse large B cell lymphomas, 1 with nasopharyngeal and 1 with gastric cancer. The median age was 57 (41-79) years. Grade 1 to 2 myelosuppression was observed in 3/14 patients, and Grade 4 myelosuppression in 1/14. Adverse effects on the gastrointestinal tract were documented in 5/14 patients, and were Grade 1 to Grade 3. No treatment related death was documented. Regarding CIM, the median response time to mouth rinse of G-CSF was 2 (1-5) days, and all patients with CIM demonstrated a positive response. **Conclusions:** Mouth-rinse with G-CSF proved to be safe and effective in treating patients with advanced cancers and CIM. However, further randomized controlled studies should be conducted to clarify the effectiveness of this treatment with other lesions.

**Keywords:** Mouth-rinse with G-CSF - chemotherapy induced oral mucositis

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## Introduction

One common side effect of chemotherapy is oral mucositis with an occurrence rate of 40-100%, depending on the type of cancer, chemotherapeutic medications, age of patient, neutrophil count, and availability of oral care (Raber-Durlacher et al., 2000; Mosel et al., 2011).

Cancer patients first reported symptoms of chemotherapy-induced mucositis (CIM) and diagnosed with CIM usually within 3-5 days after initiation of chemotherapy, and the symptom of CIM could reach a peak within 7-14 days. The course of CIM usually could last nearly 3 weeks (Loprinzi et al., 1999). CIM is associated with serials of complications, eg., oral pain, that will adversely affect nutrition, speaking, function and quality of life of patients. CIM is also linked with susceptibility to septicemia especially in conditions of neutrocytopenia. Thus, CIM could consequently result in hospitalization, increased treatment cost and delayed

optimal treatment due to restrictions on dosage of chemotherapeutic agents (Raber-Durlacher et al., 2000; Mosel et al., 2011).

A lot of medications have been attempted to treat CIM including basic oral care, eg., brushing, flossing, dental visits before and during the treatment and usage of mouth-washes, cryotherapy, as well as anti-inflammatory, antimicrobial and antiseptic agents, vitamins, cytokines, immune regulator, herbal medicine, etc (McGuire et al., 2013; Nicolatou-Galitis et al., 2013; Raber-Durlacher et al., 2013; Saunders et al., 2013).

Granulocyte colony-stimulating factor (G-CSF) is a cytokines used as hematopoietic growth factor that could stimulate the development of granulocyte (Plevova et al., 1999). G-CSF has been shown to promote wound healing in animal studies (Jyung et al., 1994). However, clinical studies on the effectiveness of mouth rinse medication when treating patients with CIM who received standard or high dose chemotherapy are mainly focused on GM-CSF

(Dazzi et al., 2003; van der Lelie et al., 2001; Cartee et al., 1995). In a recent study on the effectiveness of GM-CSF in reducing occurrence of oral mucositis, (Dazzi et al., 2003), patients were instructed to rinse for 1 min with 150µg/day of GM-CSF in 100 cm<sup>3</sup> of sterile water in four doses per day. Furthermore, patients in both treatment and control groups received conventional prophylaxis with chlorhexidine 0.2% mouth rinse and amphotericin B (Dazzi et al., 2003). The result of this study suggested that prophylaxis with GM-CSF mouth wash could not help to reduce the severity of mucositis in the setting of this study (Dazzi et al., 2003).

According to this background, it is obvious that insufficient studies were conducted to investigate the treatment effect of G-CSF for patients with CIM. We hypothesize that mouth-rinse with G-CSF could be an effective medication in treating cancer patients with CIM.

## Materials and Methods

### Eligibility criteria

**Patients:** Patients recruited in this study were required to be pathologically/ cytologically diagnosed with cancer in Jiangsu Cancer Hospital & Research Institute; to sign an informed consent before treatment; to expose to long term chemotherapy and supportive care, and were diagnosed with oral mucositis; to have a score of Karnofsky Performance Status (KPS) ≥ 60 with expectancy life span more than 3 months; to be classified with no contraindications for chemotherapy; to have a routine blood test and oral examination performed 0 to 3 days before and after chemotherapy, and normal hematopoietic function as evidenced by white blood cell count 3000/ul and platelet count 100000/ul, normal hepatic function test (aspartate aminotransaminase and alanine aminotransferase less than 1.5 times of the upper limit of normal values), renal function test (serum total bilirubin < 1.5mg/dl and creatinine < 1.5mg/dl). Exclusion criteria included history of alcoholic intoxication, diabetes, and patients who were pregnant or nursing. Chemotherapy was administered according to NCCN guideline. Mouth-rinse with G-CSF (JiSaiXin, produced by NCPC

Biotechnology CO., LTD) at a dosage of 150-300ug plus 100ml-500ml normal saline was started from the time of oral mucositis was confirmed and continuously used for at least 7 days as one course. After at least two courses of treatment, safety and effectiveness were evaluated. We have enough experience in conducting medical researches, and have published some results elsewhere (Chen et al., 2014; Chen et al., 2014; Cao et al., 2014; Cui et al., 2014; Huang et al., 2014; Huang et al., 2014; Ji et al., 2014; Liu et al., 2014; Liu et al., 2014; Lu et al., 2014; Qian et al., 2014; Tian et al., 2014; 2014; Xiao et al., 2014; Xiao et al., 2014; Xu et al., 2014; Xu et al., 2014; Xu et al., 2014; Xu et al., 2014; Wang et al., 2014; Wu et al., 2014; Cui et al., 2015; Huang et al., 2015; Huang et al., 2015; Li et al., 2015; Liu et al., 2015; Liu et al., 2015; Qian et al., 2015; Shen et al., 2015; Shi et al., 2015; Sun et al., 2015; Xu et al., 2015; Xu et al., 2015; Xu et al., 2015; Xu et al., 2015; Wang et al., 2015; Wu et al., 2015; Wu et al., 2015; Yang et al., 2015; Zhou et al., 2015)

### Toxicity Evaluation

The incidence rates of toxicity in this study were assessed at baseline and respectively after two cycles of treatment, the grade of toxicities was determined according to The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3).

## Results

There were 7 female and 7 male patients with advanced cancer recruited into this study, including 5 patients with colorectal, 2 patients with lung, 1 patient with gastric, 1 patient with cervical and 1 patient with pancreatic cancer, as well as 2 patients with diffuse large B cell lymphoma, 1 patient with nasopharyngeal and 1 patient with gastric cancer (Table 1). The median age of patients was 57 (41-79) years. Incidences of Grade 1 to 2 myelosuppression was observed in 3/14 patients, and Grade 4 myelosuppression was observed in 1/14 patient. Adverse effects on the gastrointestinal tract were documented in 5/14 patients, and were Grade 1 to Grade 3. No treatment related death

**Table 1. Characteristics of Recruited Patients**

Hospital registration number	Gender (Male/Female)	Age(year)	Diagnosis	Stage of disease	Chemotherapy	Duration of response to mouth rinse with G-CSF (days)
266241	Female	61	Pancreatic cancer	IV	FOLFOXIRI	3
265135	Male	52	Colon cancer	Dukes C	FOLFOX	2
262901	Male	57	Rectal cancer	Dukes C	FOLFOX	2
250674	Female	52	Lung adenocarcinoma	IV	Pemtrexed+Docetaxel+Oxaliplatin	1
265320	Male	77	Colon cancer	IV	FOLFOX	2
265587	Male	41	Gastric cancer	IV	Docetaxel+Oxaliplatin+TS-1	2
266345	Female	58	Diffuse large B cell lymphoma	II	CHOP	3
195410	Female	62	Colon cancer	IV	FOLFOXIRI	1
265863	Male	46	Small cell lung cancer	limited	CPT-11+Nedaplatin	4
243887	Female	79	Colon cancer	IV	FOLFOX	2
194256	Female	54	Cervical cancer	IV	Paclitaxel+Nedaplatin+5-Fu+CF	1
210374	Male	62	Diffuse large B cell lymphoma	III	ECHOP	3
267091	Male	58	Head and neck cancer	IV	Paclitaxel+Nedaplatin+TS-1	4
179540	Female	48	Nasopharyngeal cancer	IV	Paclitaxel+Nedaplatin	5

was documented. Regarding oral mucositis, the median response time to mouth rinse of G-CSF was 2 (1-5) days, and all patients with CIM response to mouth rinse with G-CSF (response rate=100%).

## Discussion

Cancer is a group of diseases with deregulated growth of abnormal cells. The reason for this uncontrolled growth is a series of mutations that cause aberrant expression of gene products essential for regulating proliferation, survival, and growth activities of cells; and further, cause basic biological changes of cells: the ability to respond to growth signals, engage cell death programs to eliminate unnecessary, excess or damaged cells, and the formation of new blood vessels and ability to invade tissue. Thus, clinicians and researchers try to find effective therapeutic approaches that could eliminate cancerous cells, meanwhile protecting normal, healthy tissues. In the field of current cancer treatment—chemo-, or radiation therapy, is one of the most commonly used methods. However, one important problem of chemo-, or radiation therapy is that these treatments are associated with various toxicities, including CIM (Kalyanaraman B et al., 2002; Naumov GN et al., 2003).

Regarding the treatment for CIM, oral care is considered as essential for cancer patients with CIM. A meta-analysis performed by Stokman et al. concluded that systemic G (M)-CSF might prevent oral mucositis (Stokman et al., 2006). Previous studies suggested evidence of GM-CSF mouthwash for the prevention of oral mucositis is controversial (Dazzi et al., 2003 ; Nicolatou-Galitis et al., 2013). A clinical study by using GM-CSF mouthwashes to treat patients with CIM in metastatic breast cancer found no clear benefit (Cartee et al., 1995). And further, evidence from randomized controlled study suggested that GM-CSF mouth washes are not effective to prevent oral mucositis (van der Lelie et al., 2001). However, there are also evidences from case series suggesting effectiveness of GM-CSF mouth washes on mucositis in patients with head and neck cancer (Nicolatou et al., 1998; Nicolatou-Galitis et al., 2001), and were verified by other studies (Saarilahti et al., 2002; Mantovani et al., 2003). Several studies addressed the use of GM-CSF mouth washes for the treatment of established mucositis in patients receiving chemo- radiotherapy for head and neck tumors, HSCT and chemotherapy (Rovirosa et al., 1998; Mantovani et al., 2003; Ibrahim et al., 1997; Hejna et al., 2001; Bez et al., 1999; Valcarcel et al., 2002; ). Thus, it was supposed that GM-CSF mouth rinses could be used for prevention and treatment for patients with chemotherapy. On the other side, systemically infused GM-CSF was also tested for patients with CIM. One study reported a benefit from systemically infused GM-CSF in treating patients with head and neck cancer and CIM (Chi et al., 1995; Kannan et al., 1997 ; Rosso et al., 1997; Wagner et al., 1999; McAleese et al., 2006), however was not confirmed by others (Ryu et al., 2007; Makkonen et al., 2000). Therefore, it was suggested that systemic infusion of GM-CSF at present should not be recommended for patients with CIM.

In terms of G-CSF, according to previous researches, it is not suggested that the use of subcutaneous G-CSF is able to prevent oral mucositis in head and neck cancers patients treated with chemo-, or radiotherapy (Abitbol et al., 1997; Mascarin et al., 1999). Only one study on the use of systemic

G-CSF for the prevention of CIM for head and neck cancers has been published (Su et al., 2006). This study reported a non-significant trend for a beneficial effect of this intervention but was closed prematurely because of low accrual. Worthington et al. concluded that there is weak evidence that systemic or topical G-CSF may be beneficial for the prevention of severe oral mucositis in head and neck cancer patients undergoing radiotherapy (Worthington et al., 2010). Thus, it was concluded that no guideline could be provided for the use of subcutaneous G-CSF for the prevention of CIM (Katano et al., 1995 ; Viens et al., 1996). In addition, no guideline could be provided for the use of a G-CSF mouthwash for the prevention of CIM (Karthaus et al., 1998).

In this study, our purpose is to assess the safety and effectiveness of mouth-rinse with G-CSF (JiSaiXin, produced by NCPC Biotechnology CO., LTD) in treating patients with CIM. We recruited 7 female and 7 male patients with advanced cancer into this study, including 5 patients with colorectal, 2 patients with lung, 1 patient with gastric, 1 patient with cervical and 1 patient with pancreatic cancer, as well as 2 patients with diffuse large B cell lymphoma, 1 patient with nasopharyngeal and 1 patient with gastric cancer. The median age of patients was 57 (41-79) years. Mouth-rinse with G-CSF was started at a dosage of 150-300ug plus 100ml-500ml normal saline from the time of oral mucositis and was confirmed and continuously used for 7 days as one course. As a result, it was suggested that the incidence of Grade 1 to 2 myelosuppression was observed in 3/14 patients, and Grade 4 myelosuppression was observed in 1/14 patient. Adverse effects on the gastrointestinal tract were documented in 5/14 patients, and were Grade 1 to Grade 3. No treatment related death was documented. In terms of oral mucositis, the median response time to mouth rinse of G-CSF was 2 (1-5) days, and the response rate of mouth rinse of G-CSF was 100%. In conclusion, our current study suggested that mouth-rinse with G-CSF combined with chemotherapy was safe and effective in treating advanced cancers patients with CIM. However, further randomized controlled studies should be conducted to clarify the effectiveness of this treatment with others.

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