Yonago Acta Medica 2020;63(3):183–187 doi: 10.33160/yam.2020.08.007

The effect of Hangeshashinto on Oral Mucositis Caused by Induction Chemotherapy in Patients with Head and Neck Cancer

Kenkichiro Taira, Kazunori Fujiwara, Takahiro Fukuhara, Satoshi Koyama and Hiromi Takeuchi

Division of Otolaryngology, Head and Neck Surgery, Department of Sensory and Motor Organs, School of Medicine, Faculty of Medicine, Tottori University, Yonago 683-8504, Japan

ABSTRACT

Background Oral mucositis (OM) is a side effect of chemotherapy in head and neck cancer. Severe OM often has a large impact on quality of life. Therefore, the treatment of OM during chemotherapy is very important. It was recently reported that Hangeshashinto (TJ-14), a Japanese traditional medicine (Kampo), is effective for OM caused by fluorinated pyrimidine-based agents used in colon cancer. We investigated the efficacy of TJ-14 for OM.

Methods We enrolled patients with head and neck cancer who were treated with induction chemotherapy between September 2014 and March 2016. In this double-blind trial, patients were randomly assigned to the TJ-14 group or placebo group. Patients were instructed to dissolve 2.5 g of TJ-14 or placebo in 100 ml of drinking water, rinse their mouths with the solution for 30 s and then spit it out. They were not allowed to eat anything for 30 minutes before or after using the mouthwash.

Results The incidence of ≥ grade 2 OM was 37.5% (three patients) in the TJ-14 group and 50.0% (four patients) in the placebo group, with no significant difference between the two groups. The mean day of onset was 9.7 in the TJ-14 group and 6.7 in the placebo group. The mean duration of ≥ grade 2 OM was 1.3 days in the TJ-14 group and 3.7 days in the placebo group. Thus TJ-14 significantly reduced the duration of ≥ grade 2 OM.

Conclusion Treatment of OM with TJ-14 was associated with a statistically significant reduction in the duration of ≥ grade 2 OM compared to placebo. Gargling with TJ-14 is a safe and effective method of administering the drug to patients with head and neck cancer.

Key words chemotherapy; gargling; Hangeshashinto; head and neck cancer; oral mucositis

Corresponding author: Kenkichiro Taira, MD
kenkichiro.t@tottori-u.ac.jp
Received 2020 June 16
Accepted 2020 July 6
Online published 2020 August 20

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; OM, oral mucositis; PGE2, prostaglandin E2; QOL, quality of life; TJ-14, Hangeshashinto; TPF, docetaxel-cisplatin-5-FU

Chemotherapy is an essential treatment for head and neck cancer, and the docetaxel-cisplatin-5-fluorouracil (TPF) regimen is common.[1, 2] Oral mucositis (OM) is one of the side effects of chemotherapy.[3] Severe OM often makes adequate food intake impossible, which impairs patients' nutritional status and quality of life (QOL). Further, pain associated with severe OM can reduce therapeutic compliance or induce dose-limiting toxicity, necessitating treatment modification or interruption, and may thereby eventually affect the outcome of cancer therapy.[4] Several means of treating OM have been reported, including mouthwash containing lidocaine[5] or the combination of soluble prednisolone and nystatin,[6] but these only improved OM symptoms temporarily.

It was recently reported that Hangeshashinto (TJ-14), a Japanese traditional medicine (Kampo), was effective for OM caused by fluorinated pyrimidine-based agents, including 5-fluorouracil, that are used in colon cancer therapies.[7, 8] While several treatments for OM are temporarily effective as symptomatic therapy, none have been proven to maintain long-term efficacy. The aims of this study were to assess the efficacy of TJ-14 for the prevention and/or treatment of chemotherapy-induced OM in a randomized, double-blind, placebo-controlled exploratory clinical trial in patients with head and neck cancer.

MATERIALS AND METHODS

Patients

In this study, we enrolled patients who underwent chemotherapy at Tottori University Hospital between September 2014 and March 2016 and who met the following criteria: (i) aged 20 years or older; (ii) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and (iii) diagnosis of pharyngeal, laryngeal, oral or maxillary sinus squamous cell carcinoma, classified as T2-T4a according to the Union for International Cancer Control classification system. All patients gave informed consent. The exclusion criteria were failure to complete chemotherapy, a history of allergy to Kampo medicine, and low performance status (≥ 2). The study protocol consisted of patients who underwent the first course of induction chemotherapy.

Study protocol

Both TJ-14 and placebo were administered at a dose of 2.5 g after each meal (three times per day), for a total daily dose of 7.5 g. Lactose was used as placebo.

Lactose is safe for the patients because there is no report that lactose has any influence on the oral mucositis. Both drugs were wrapped in white paper so they could not be seen. In this double-blind, placebo-controlled, randomized study, patients were divided into two groups using the Japanese Industrial Standards random number table. Administration of study treatment began on the first day of chemotherapy and was continued for 14 days. Patients were instructed to dissolve 2.5 g of TJ-14 or placebo in 100 ml of drinking water, to rinse their mouths with the solution for 30 s, and then to spit it out. They were not allowed to eat anything for 30 minutes before or after using the mouthwash. They were allowed to use lidocaine gargles, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or opioids if needed to treat severe oral pain caused by OM.

The TPF regimen consisted of docetaxel 75 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 4, and 5-fluorouracil 1000 mg/m^2 from days 1–5. The oral cavity was observed daily from the first day of chemotherapy until OM resolved completely.

No other prophylactic mouthwashes or treatments for OM were allowed in this clinical trial. The severity of OM was assessed using the National Cancer Institute Common Criteria for Adverse Events criteria.

The primary endpoints were the duration of ≥ grade 2 OM and the maximum grade of OM. The secondary endpoints were the incidence of OM, the day of OM onset, the total duration of OM, and the incidence of adverse events due to chemotherapy.

Statistical analysis

Statistical analyses were performed using SAS University Edition for Windows, release 9.3 (SAS Institute, Cary, NC). The incidences of both OM and adverse events due to chemotherapy were calculated by Fisher's exact test. The duration of ≥ grade 2 OM, the maximum grade of OM, the day of OM onset, and the total duration of OM were evaluated by the Mann-Whitney *U* test.

Ethical considerations

The study data and informed consent were obtained in accordance with the Declaration of Helsinki and were approved by the Ethics Review Board of Tottori University Hospital; the approval number was 2478.

RESULTS

Sixteen patients were included in this study; there were eight patients (seven males, one female) in the TJ-14 group, and eight (seven males, one female) in the placebo group. The median age was 63.2 years (range, 49–79 years). All patients had histologically confirmed squamous cell carcinoma. Patient characteristics, including the primary tumor location and clinical stage, are shown for both groups in Table 1. No patients developed distant metastasis. TPF was completed in all patients. In the TJ-14 group, one patient had to reduce the dose to 75% and another required a reduction to 80%, in both cases due to old age.

The overall incidence of OM was 75% (six patients) in the TJ-14 group and 87.5% (seven patients) in the placebo group. The incidence of ≥ grade 2 OM was 37.5% (three patients) in the TJ-14 group and 50.0% (four patients) in the placebo group, indicating no significant difference between the groups. As shown in Table 2, the mean day of onset was day 9.7 in the TJ-14 group and day 6.7 in the placebo group.

The mean duration of ≥ grade 2 OM was 1.3 days in the TJ-14 group and 3.7 days in the placebo group. TJ-14 significantly reduced the duration of ≥ grade 2 OM. Table 3 shows the adverse events associated with TPF; these did not differ significantly between the two groups. No patients in the TJ-14 group experienced adverse events related to the drug.

DISCUSSION

There have been several reports that TJ-14 is effective for OM-induced chemoradiotherapy; however, there have been no reports demonstrating that TJ-14 is effective for OM-induced by induction chemotherapy in head and neck cancer.[7, 9] Reducing the incidence of adverse events related to chemotherapy facilitates the treatment. Many regimens, including TPF, cause widespread OM throughout the oral cavity, and pain due to OM can make oral intake difficult, which may reduce physical strength and immunity. In some cases, this can prevent continuation of treatment. It is therefore important to alleviate OM symptoms, but no effective treatment has been established.

TJ-14 has been shown to reduce the rate of severe, grade 3/4 OM induced by radiotherapy and radiochemotherapy in head and neck cancer.[9, 10] There are some reports that grade 3/4 OM occurred in more than 30% patients who underwent TPF. However, no reports have shown that TJ-14 is effective for OM induced by chemotherapy alone in head and neck cancer. Our study examined the effects of OM in this setting, and demonstrated statistical significance in terms of reducing the

Table 1. Patients characteristic

Case no.		Subsite	TNM	Age (yr)	Gender
1	T	Oropharynx	T4aN0M0	53	M
2	T	Oropharynx	T4aN2cM0	62	M
3	T	Hypopharynx	T3N2bM0	83	M
4	T	Hypopharynx	T4aN2cM0	62	F
5	T	Oropharynx	T4aN1M0	62	M
6	T	Oropharynx	T4aN2cM0	54	M
7	T	Hypopharynx	T4aN2cM0	63	M
8	T	Oropharynx	T3N2cM0	73	M
9	P	Hypopharynx	T4aN2cM0	58	M
10	P	Oropharynx	T4aN2cM0	64	M
11	P	Larynx	T2N0M0	72	M
12	P	Hypopharynx	T4aN2cM0	52	M
13	P	Hypopharynx	T2N2cM0	49	M
14	P	Maxillary sinus	T3N0M0	65	F
15	P	Maxillary sinus	T4aN0M0	79	M
16	P	Oropharynx	T3N3M0	67	M

TNM staging system is defined by Union for International Cancer Control classification system. F, female; M, male; P, placebo; T, TJ-14; yr, years.

Table 2. Comparison between TJ-14 and placebo for OM

	TJ-14	Placebo	*P* value
Rate of OM (%)	75.0	87.5	0.600
Rate of OM ≥ G2 (%) (G2/G3/G4)	37.5 (37.5/0/0)	50.0 (25.0/25.0/0)	0.580
On set (day)	9.7	6.7	0.258
Duration of OM (day)	4.7	6.7	0.522
Duration of OM ≥ G2 (day)	1.7	3.7	0.039

G2, grade 2; G3, grade 3; G4, grade 4.

Table 3. Adverse effect of induction chemotherapy instead of OM

Adverse effect ≥ grade 2	TJ-14 ($n = 8$)	Placebo ($n = 8$)
Neutropenia	7	6
Thrombocytopenia	0	1
Anemia	1	0
Diarrhea	6	5
Loss weight	0	1
Gain weight	1	1

duration of severe, ≥ grade 2 OM compared to placebo.

Pain relief for OM is often achieved using NSAIDs, narcotics, and/or local anesthesia, but these drugs have side effects such as gastric mucosal disorders, nausea, and taste disorders, all of which can reduce oral intake.[11–13] In this study, TJ-14 had no side effects. TJ-14 contains Coptidis Rhizoma and Glycyrrhizae Radix, which have been shown to induce side effects such as pseudoaldosteronism and herbal medicine-induced pneumonitis.[14, 15] One study reported that TJ-14 may have been associated with liver injury.[9, 15] More importantly, however, previous studies that demonstrated side effects used oral administration of TJ-14. In our study, patients gargled the medication, which is a safer and more effective method of administration for head and neck cancer patients.

TJ-14 is composed of seven herbal compounds: Pinelliae Tuber, Scutellariae Radix, Zingiberis Rhizoma, Ginseng Radix, Glycyrrhizae Radix, Zizyphi Fructus, and Coptidis Rhizoma. Several herbal substances have known mechanisms that reduce the severity of OM. It has been reported that Gingerol in Zingiberis Rhizoma and Baicalin in Coptidis Rhizoma suppress the production of prostaglandin E2 (PGE2), an inflammatory mediator that induces mucosal apoptosis and thereby causes OM.[16–19] TJ-14 as a whole also suppresses the expression of PGE2.[20] The antibacterial action of Berbelin in Coptidis Rhizoma is effective for preventing secondary infections by oral bacteria, which can worsen the severity of OM.[20, 21]

It has been suggested that the development of OM during chemotherapy occurs due to the cyclooxygenase pathway, which mediates tissue injury and pain by upregulating PGE2 and proinflammatory cytokines.[15] TJ-14 has been reported to have anti-inflammatory effects in both in vivo and in vitro studies.[22, 23] We speculate that the effects of TJ-14 in head and neck cancer are similar to those in other cancers. We confirm in this study that TJ-14 is effective for OM induced by TPF in patients with head and neck cancer and shorten the duration of ≥ grade 2 OM.

When patients experience relief from OM-related pain, they can ingest food orally and do not require nasal tube feeding or parenteral nutrition for nutritional management. Thus, the reduced duration of OM morbidity should help improve patient QOL.

This study has several limitations. First, since this study size was small, the difference between the treatment and placebo groups may not in fact have been significant. Second, the distribution of primary disease sites was not necessarily the same between the two groups, and different sites might be associated with differing levels of pain.

In conclusion, TJ-14 significantly inhibited ≥ grade 2 OM induced by chemotherapy in patients with head and neck cancer. Further studies are required to fully understand the biological activity of TJ-14 against OM in this population.

The authors declare no conflict of interest.

REFERENCES

1 Gau M, Karabajakian A, Reverdy T, Neidhardt EM, Fayette J. Induction chemotherapy in head and neck cancers: results and controversies. Oral Oncol. 2019;95:164-9. DOI: 10.1016/j.oraloncology.2019.06.015, PMID: 31345386

2 Lorch JH, Goloubeva O, Haddad RI, Cullen K, Sarlis N, Tishler R, et al.; TAX 324 Study Group. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol. 2011;12:153-9. DOI: 10.1016/S1470-2045(10)70279-5, PMID: 21233014

3 Bhide SA, Gulliford S, Schick U, Miah A, Zaidi S, Newbold K, et al. Dose–response analysis of acute oral mucositis and pharyngeal dysphagia in patients receiving induction chemotherapy followed by concomitant chemo-IMRT for head and neck cancer. Radiother Oncol. 2012;103:88-91. DOI: 10.1016/j.radonc.2011.12.027, PMID: 22280809

4 Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al.; Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury. Cancer. 2004;100(suppl):1995-2025. DOI: 10.1002/cncr.20162, PMID: 15108222

5 Silva FC, Marto JM, Salgado A, Machado P, Silva AN, Almeida AJ. Nystatin and lidocaine pastilles for the local treatment of oral mucositis. Pharm Dev Technol. 2017;22:266-74. DOI: 10.1080/10837450.2016.1221424, PMID: 27499389

6 Cidon EU. Chemotherapy induced oral mucositis: prevention is possible. Linchuang Zhongliuxue Zazhi. 2018;7:6. DOI: 10.21037/cco.2017.10.01, PMID: 29156889

7 Matsuda C, Munemoto Y, Mishima H, Nagata N, Oshiro M, Kataoka M, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. Cancer Chemother Pharmacol. 2015;76:97-103. DOI: 10.1007/s00280-015-2767-y, PMID: 25983022

8 Kono T, Satomi M, Chisato N, Ebisawa Y, Suno M, Asama T, et al. Topical Application of Hangeshashinto (TJ-14) in the Treatment of Chemotherapy-Induced Oral Mucositis. World J Oncol. 2010;1:232-5. PMID: 29147213

9 Yamashita T, Araki K, Tomifuji M, Kamide D, Tanaka Y, Shiotani A. A traditional Japanese medicine—Hangeshashinto (TJ-14)—alleviates chemoradiation-induced mucositis and improves rates of treatment completion. Support Care Cancer. 2015;23:29-35. DOI: 10.1007/s00520-014-2315-z, PMID: 24943276

10 Kamide D, Yamashita T, Araki K, Tomifuji M, Shiotani A. Hangeshashinto (TJ-14) prevents radiation-induced mucositis by suppressing cyclooxygenase-2 expression and chemotaxis of inflammatory cells. Clin Transl Oncol. 2017;19:1329-36. DOI: 10.1007/s12094-017-1672-8, PMID: 28516399

11 Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther. 2013;15(suppl 3):S3. DOI: 10.1186/ar4175, PMID: 24267289

12 de Boer HD, Detriche O, Forget P. Opioid-related side effects: postoperative ileus, urinary retention, nausea and vomiting, and shivering. A review of the literature. Best Pract Res Clin Anaesthesiol. 2017;31:499-504. DOI: 10.1016/j.bpa.2017.07.002, PMID: 29739538

13 Asante MA, Northfield TC. Variation in taste of topical lignocaine anaesthesia for gastroscopy. Aliment Pharmacol Ther. 1998;12:685-6. DOI: 10.1046/j.1365-2036.1998.00355.x, PMID: 9701534

14 Enomoto Y, Nakamura Y, Enomoto N, Fujisawa T, Inui N, Suda T. Japanese herbal medicine-induced pneumonitis: A review of 73 patients. Respir Investig. 2017;55:138-44. DOI: 10.1016/j.resinv.2016.11.007, PMID: 28274529
15 Shimada Y, Fujimoto M, Nogami T, Watari H. Adverse Events Associated with Ethical Kampo Formulations: Analysis of the Domestic Adverse-Event Data Reports of the Ministry of Health, Labor, and Welfare in Japan. Evid Based Complement Alternat Med. 2019;2019:1-14. DOI: 10.1155/2019/1643804, PMID: 31118950
16 Kono T, Kaneko A, Matsumoto C, Miyagi C, Ohbuchi K, Mizuhara Y, et al. Multitargeted effects of hangeshashinto for treatment of chemotherapy-induced oral mucositis on inducible prostaglandin E2 production in human oral keratinocytes. Integr Cancer Ther. 2014;13:435-45. DOI: 10.1177/1534735413520035, PMID: 24501112
17 Chi YS, Kim HP. Suppression of cyclooxygenase-2 expression of skin fibroblasts by wogonin, a plant flavone from Scutellaria radix. Prostaglandins Leukot Essent Fatty Acids. 2005;72:59-66. DOI: 10.1016/j.plefa.2004.04.009, PMID: 15589400
18 Feng AW, Gao W, Zhou GR, Yu R, Li N, Huang XL, et al. Berberine ameliorates COX-2 expression in rat small intestinal mucosa partially through PPARγ pathway during acute endotoxemia. Int Immunopharmacol. 2012;12:182-8. DOI: 10.1016/j.intimp.2011.11.009, PMID: 22155099
19 Pan MH, Hsieh MC, Hsu PC, Ho SY, Lai CS, Wu H, et al. 6-Shogaol suppressed lipopolysaccharide-induced up-expression of iNOS and COX-2 in murine macrophages. Mol Nutr Food Res. 2008;52:1467-77. DOI: 10.1002/mnfr.200700515, PMID: 18683823
20 Samosorn S, Tanwirat B, Muhamad N, Casadei G, Tomkiewicz D, Lewis K, et al. Antibacterial activity of berberine-NorA pump inhibitor hybrids with a methylene ether linking group. Bioorg Med Chem. 2009;17:3866-72. DOI: 10.1016/j.bmc.2009.04.028, PMID: 19419877
21 Rohrer U, Kunz EM, Lenkeit K, Schaffner W, Meyer J. Antimicrobial activity of Mahonia aquifolium and two of its alkaloids against oral bacteria. Schweiz Monatsschr Zahnmed. 2007;117:1126-31. PMID: 18072463
22 Wang HM, Lin CY, Hsieh CH, Hsu CL, Fan KH, Chang JTC, et al. Induction chemotherapy with dose-modified docetaxel, cisplatin, and 5-fluorouracil in Asian patients with borderline resectable or unresectable head and neck cancer. J Formos Med Assoc. 2017;116:185-92. DOI: 10.1016/j.jfma.2016.03.005, PMID: 27133181
23 Rampino M, Bacigalupo A, Russi E, Schena M, Lastrucci L, Iotti C, et al. Efficacy and feasibility of induction chemotherapy and radiotherapy plus cetuximab in head and neck cancer. Anticancer Res. 2012;32:195-9. PMID: 22213307