INTRODUCTION

Concurrent chemoradiotherapy is one of the standard therapeutic modalities in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) and has contributed to the improvement of survival and functional outcomes. However, concurrent chemotherapy and chemoradiotherapy often shows significantly enhanced acute toxicity, particularly mucositis of oral cavity, pharynx and larynx. It is reported that acute mucositis occurs 100% of HNSCC patients who have undergone concurrent chemoradiotherapy, presenting significant clinical and economic problem. Resulting breaks in radiation therapy or concurrently administered chemotherapy from the pain or the swallowing dysfunction associated with radiation-induced mucositis can influence treatment outcomes and the period of hospitalization. Although many kinds of cares and treatments have been applied to prevent or alleviate radiation-induced mucositis, the efficacy is limited thus far 9, 10. Hangeshashinto-TJ14 is a Japanese kampo medicine made of a mixture of seven herbs (Pueraria tuberosa, Spondias dulcis, Rhizoma Coptidis, Gynostemma驾车, Panax ginseng, Lycopus carolinianus and Zingiber officinale). It is often used to treat acute and chronic gastrointestinal catarrh, fermentative diarrhea, acute gastroenteritis and intractable oral mucositis. Although recently it is shown that TJ-14 is effective for the chemotherapy-induced oral mucositis or diarrhea, there is no report of the use of TJ-14 against the chemoradiation-induced mucositis.

Therefore we have investigated the preventive effect of TJ-14 for chemoradiation-induced mucositis by comparing patients received TJ-14 treatment with control patients who did not undergo TJ-14 treatment in HNSCC treated with (chemo)radiotherapy.

PATIENTS AND METHODS

We started using TJ-14 to prevent radiation-induced mucositis in May 2011. Therefore its preventive effect for mucositis were investigated by comparing the cases treated before May 2011 with the cases after May 2011. All patients were diagnosed HNSCC and received total radiation dose of more than 60Gy to oral cavity, pharynx and larynx with or without concurrent chemotherapy. Concurrently administered chemotherapeutic agents were Cisplatin (75mg/m2 IV infusion intrawise 3 times during radiotherapy) or Docetaxel (10mg/m2 weekly, 6 times during radiotherapy). Between May 2011 and April 2012, 22 patients (Treatment Group with TJ-14) with HNSCC conducted radiotherapy with or without concurrent chemotherapy. We defined the medical center of National Defense Medical College of Japan as the TJ-14 for the purpose of preventing mucositis. On the other hand, Between May 2010 to April 2011, 19 HNSCC patients (Control Group) received radiotherapy with or without concurrent chemotherapy were not treated with TJ-14.

The characteristics of the patients of each group are summarized in Table 1. More intensive regimen (concurrent with cisplatin) and higher radiation dose were used in TJ-14 treatment group than control group. The way to administer TJ-14 is as follows. The patients rinsed with a 100ml oral rinse solution with components of TJ-14 gargle was useful for maintaining nutrition status during (chemo)radiotherapy. Treatment group with TJ-14 gargle against radiation mucositis shows significantly enhanced acute toxicity, particularly improvement of survival and functional preservation in head and neck squamous cell carcinoma (HNSCC) and has contributed to the management of patients. It is often used to treat acute and chronic gastrointestinal catarrh, fermentative diarrhea, acute gastroenteritis and intractable oral mucositis. Although recently it is shown that TJ-14 is effective for the chemotherapy-induced oral mucositis or diarrhea, there is no report of the use of TJ-14 against the chemoradiation-induced mucositis. 11, 12

RESULTS

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DISCUSSION

Fig. 4 The pathogenic mechanisms of chemoradiation-induced mucositis and action mechanisms of TJ-14

Reactive oxygen species generated by radiation induce transcription factors such as NF-κB and STAT3, which enhances the expression of proinflammatory cytokine interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF)-α. Many of these proteins induce apoptosis of basal epithelial cells in the mucosa. Consequently, suppressed mucosal renewal leads to mucosal thinning and ulceration. Ucleration of oral mucosa, in turn, causes pain or swallowing dysfunction and also forms bacterial colonization. Leukospenia and suppression of the immune system caused by commonly used chemotherapy enhances the formation of bacterial colonization. These mechanisms are considered one of the major causes for deterioration of mucositis. 13, 14

It is reported that TJ-14 has anti-inflammatory effect through the suppression of COX-2 and PGE2 15, 16, which is a crucial mediator of inflammatory pain sensitization. In addition, Lactobacillus Rhamnosus which is extracted in TJ-14 gargle was shown to have anti-inflammatory effects 17, 18. Furthermore, Berberine which is the main ingredient of Coptidis Rhamnos is well-known to possess a strong and wide-spectrum antimicrobial activity. 19, 20. Cross marks in the figure shows the action sites of TJ-14 predicted from the facts indicated above.

SUMMARY

TJ-14 gargle was able to alleviate (chemo)radiation-induced mucositis in head and neck cancer: TJ-14 gargle treatment reduced the percentage of cases with severe mucositis (≥ Grade 3) from 26.3% to 4.5%.

TJ-14 gargle was also useful for the improvement of treatment compliance of (chemo)radiotherapy in head and neck cancer. In addition, TJ-14 treatment contributed to maintenance of nutrition status during (chemo)radiotherapy.

Our findings from the retrospective study support the beneficial effects of TJ-14 for (chemo)radiotherapy-induced mucositis in head and neck cancer. To confirm the findings, the usefulness of TJ-14 for (chemo)radiotherapy-induced oral and pharyngeal mucositis must be studied further by prospective randomized trials.