INTRODUCTION

Oral mucositis is a common complication of systemic chemotherapy as well as radiotherapy for cancer. Severe chemotherapy-induced oral mucositis (COM) impairs oral and esophageal functions, and seriously affects nutrition and quality of life of the patients. Consequently, oral mucositis can result in therapeutic non-compliance or become a dose-limiting toxicity that requires treatment modifications or interruption and eventually affect the outcome of cancer therapy. Several reviews and clinical practice guidelines have confirmed the need for increased emphasis on the management of mucositis.

Hangeshashinto (TJ-14) is a traditional Japanese medicine containing 7 herbal crude drugs. We previously reported that a trend was observed in which TJ-14 reduced the risk of chemotherapy-induced oral mucositis (COM) in gastric cancer patients who developed grade 1 COM during the screening cycle, and that TJ-14 demonstrated a significant effect in the treatment of grade ≥2 mucositis in patients with colorectal cancer compared to the placebo.

Although these findings are limited and we could not show conclusive results of the efficacy of TJ-14 partially.
because the analysis was underpowered. And in previous trials, because of the dose-reduction of chemotherapy performed before the administration of protocol treatment and chemotherapy treatment failure during the protocol treatment, we could not evaluate the effect of TJ-14 precisely. In the present study, we will conduct a meta-analysis of patient-level data of these two randomized trials for the selected patients who did not reduce the dose of chemotherapy, to clarify the efficacy of TJ-14 in the treatment of grade ≥2 COM of patients receiving chemotherapy for gastroenterological cancer. We have described the details of this trials as the protocol paper here.

**PROTOCOL DIGEST OF THE STUDY**

**Purpose**

The purpose of the study is to evaluate the efficacy of Hangeshashinto (TJ-14) in patients with chemotherapy-induced oral mucositis (COM) for gastroenterological cancer.

**Resources**

This work is supported by the non-profit organization Epidemiological & Clinical Research Information Network (ECRIN).

**Selection of the studies**

We selected two studies, the HANGESHA-G trial and the HANGESHA-C trial6,7. We selected these two trials because they were randomized phase III trials employing the same regimen. In these two trials, eligibility criteria and treatment methods were exactly the same.

**Study Design**

All clinical data will be extracted and held centrally at the ECRIN data center. In both previously reported trials, patients who developed CTCAE grade ≥1 oral mucositis during the first screening cycle of chemotherapy were eligible for randomization. Eligible patients were centrally randomized to receive either TJ-14 or placebo during their next second cycle of chemotherapy. The patients were stratified according to age, chemotherapy regimen, institution and previous treatment for oral mucositis before randomization in a 1:1 ratio. A matched placebo, specially made and prepared was utilized to maintain blinding.

**Patients selection**

In previous trials, because of the dose-reduction of chemotherapy performed before the administration of protocol treatment and chemotherapy treatment failure during the protocol treatment, we could not evaluate the effect of TJ-14 precisely. In this study, we defined the patients who did not reduce the dose of chemotherapy as the per protocol set (PPS) population.

**Endpoints**

The primary endpoint of this study was time to remission of severe (CTCAE grade ≥2) COM to grade ≤1 in TJ-14 group compared with placebo group. Secondary endpoint was incidence of grade ≥2 COM. Moreover, identification of predictive factors of time to remission of grade ≥2 COM to grade <1 and incidence of grade ≥2 COM were estimated using Cox regression with adjustment for clinical factors.

**Statistical methods**

All clinical data will be extracted and held centrally at the ECRIN data center. The difference in the incidence of grade 2 or worse COM between the groups and its 90% confidence interval were calculated. Comparisons will be made using the chi-squared test. The baseline characteristics will be compared using the chi-squared test for categorical variables and the Wilcoxon test for continuous variables. The Kaplan-Meier method, log-rank test and Cox proportional hazard regression model will be used to assess the time to healing among the patients with COM. A hazard ratio smaller than 1 indicated that TJ-14 accelerated the healing of COM. Distributions of clinical factors, including age, sex, performance status, disease lesion, adjuvant or metastatic, and chemotherapy regimen will be described and compared across trials using ANOVA or Fisher’s exact test. The frequencies of adverse events will be compared using Fisher’s exact test. All p-values will be two-sided. The statistical analyses will be performed using the SAS software package for Windows, release 9.3 (SAS Institute, Cary, NC).

**Ethical approval**

The study data and informed consent were obtained in accordance with the Declaration of Helsinki and were approved by the Ethics Review Board of each participating institution.

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