[Short Communication]

Effects of a Camostat Mesilate Gargle on Stomatitis Caused by Molecular Target Therapy: A Case Report

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Abstract: Sorafenib is a small molecule that inhibits tumor cell proliferation and tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models. Generally, stomatitis occurs in approximately 40% of cancer patients treated with chemotherapy. In the case of sorafenib, 10% of patients develop stomatitis as a serious adverse effect. A case of serious stomatitis induced by the use of sorafenib is reported. The patient had already used rebamipide and allopurinol. Therefore, the patient was treated with camostat mesilate as an alternative. The stomatitis improved, and the associated pain was relieved. The patient's food intake and quality of life improved.

Key words: stomatitis, molecular target therapy, camostat mesilate gargle

INTRODUCTION

Stomatitis is one of the side effects of cancer chemotherapy, and patients present with pain, ulcers, and bleeding. Furthermore, the patients cannot eat, and their quality of life deteriorates considerably. This can cause interruptions in treatment or a decrease in drug doses[1]. It is considered that stomatitis is caused by free radicals from anticancer agents that destroy the organization of the oral mucosa; an infection can subsequently develop, especially since anticancer agents also decrease the white blood cell count[2, 3]. Furthermore, stomatitis caused by molecular target drugs depends on the inhibition of the biological metabolism of cells[4].

Presently, there is some evidence on which to base the treatment of stomatitis caused by cancer. For example, oral cryotherapy using ice chips prevents stomatitis induced by 5-fluorouracil (5-FU)[5]. A mouthwash with benzydamine as an anesthetic and a non-steroidal medicine with anti-inflammatory effects is more effective when used prophylactically to prevent stomatitis than when used therapeutically once stomatitis is present.

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A mouthwash including allopurinol, camostat mesilate, and rebamipide, which are able to control free radicals generated by anticancer agents, has been used[6–12]. In particular, rebamipide has been reported to be effective not only as a gargle, but also with oral administration[13].

One of the anticancer agents causing stomatitis is 5-FU. 5-FU shows an antitumor effect by phosphorylation, but the phosphorylation of 5-FU can be inhibited by allopurinol, thus decreasing its antitumor effects[7]. On the other hand, the antitumor effects of 5-FU are not decreased by camostat mesilate. Therefore, camostat mesilate gargle has become the first-choice medicine at our hospital for treating stomatitis caused by anticancer agent treatment. A case of serious stomatitis caused by oral administration of sorafenib, a molecular target drug, is described. The stomatitis was effectively treated with camostat mesilate gargle.

ETHICAL CONSIDERATIONS

The camostat mesilate gargle used in this case was approved by the institutional review board of Kashiwa City Hospital (approval number: No. 26), and was used in accordance with the Declaration of Helsinki. Furthermore, informed consent for the use of camostat mesilate gargle was obtained from the patient and the patient's family.

CLINICAL CASE

A 73-year-old female patient was diagnosed with renal cell carcinoma (clear cell type pT4 PV1a, Robsori's stage IIIA) two years ago. The patient underwent extirpation of the right kidney. After discharge from the hospital,

the patient was treated with interferon Nα (6 million units, three times a week for 15 months) as an outpatient. However, she had multiple lung metastases, abdominal lymph node metastases, and the efficacy period was 15 months. As a result, the patient was admitted to Kashiwa City Hospital to start oral administration of sorafenib tosylate, a molecular target medicine. At first, the patient was started on a small quantity of anticancer medicine, which was then increased slowly by the patient's doctor. The aim was that she would become an outpatient. The patient had high blood pressure, hyperuricemia, diabetes, hyperlipidemia, low-back pain, and anemia, but she did not take any drugs for diabetes or hyperlipidemia (Table 1).

The patient was highly motivated, and her medication adherence was good. Her height at the time of her hospitalization was 145 cm, and her weight was 60 kg. In addition, her white blood cell count was 9,200 /μl, and she was on a normal diet (1,600 kcal/day).

Progress after hospitalization and treatment: The patient started taking 200 mg/day of sorafenib. The dose was increased slowly based on the evaluation performed every three weeks. Generally, the Common Terminology Criteria for Adverse Events (CTCAE) are used for classifying stomatitis. In this case, to evaluate the seriousness of stomatitis in greater detail, we originally developed the criteria by reference to the general standard in the CTCAE v2.0 of the American National Cancer Institute (NCI) (Table 2). The judgment criteria are classified in 0.5-point increments in this original stomatitis scoring system. By adding the subjective assessment of patients, such as the ease of intake, to the objective assessment for their oral status, it seemed to be possible to describe the changes of the oral condition felt by the patients themselves, even if the objective changes were not observed in their oral cavity.

The patient developed higher blood pressure, a rash, and fever as side effects after starting sorafenib (200 mg/day). However, with symptomatic treatment and stopping of the medicine, all symptoms improved. The patient complained of pain at the tip of the tongue the day after the medicine was restarted. She was then treated with dexamethasone ointment and 4% sodium gualenate hydrate gargle three times a day, but the symptom worsened. The inflammation at the tip of the tongue became a white spot that expanded and appeared to involve the whole tongue. Furthermore, stomatitis in the form of an ulcer spread through both cheeks, and the corners of the mouth showed stomatitis. The stomatitis reached Grade 3 (Fig. 1-①). There was no change in the patient's condition. However, the patient complained of severe pain and sensitivity of the tongue. Sorafenib was discontinued for 7 days (Fig. 1-②). The stomatitis increased to Grade 3.5 from Grade 3 for only one day after sorafenib was canceled. However, the tumor decreased in size, and the blood test values indicated no major problems. Although the grade of the stomatitis decreased with discontinuation of sorafenib, sorafenib was increased to 400 mg/day while being careful about the stomatitis (Fig. 1-③). However, the stomatitis changed to 2.5 from 3 when sorafenib was restarted (Fig. 1-④). The pharmacist discussed possible drug treatment for the stomatitis with the doctor. Since the patient had been taking rebamipide, the pharmacist suggested camostat gargle (CMG). A prescription for CMG is shown in Table 3.

The stomatitis was Grade 3 when the patient started

Table 1 The patient's oral drug therapy regimen

Drug	Dose per day	Regimen
Candesartan tablet 4 mg	1 tablet	Once a day (After breakfast)
Allopurinol tablet 100 mg	1 tablet	Once a day (After breakfast)
Valsartan tablet 8 mg	1 tablet	Once a day (After breakfast)
Sodium ferrous citrate 50 mg	2 tablets	Twice a day (After breakfast and dinner)
Ascorbic acid and calcium pantothenate	2 g	Twice a day (After breakfast and dinner)
Cimetidine tablet 50 mg	2 tablets	Twice a day (After breakfast and dinner)
Etodolac tablet 100 mg	2 tablets	Twice a day (After breakfast and dinner)
Rebamipide tablet 100 mg	3 tablets	Three times a day (After an every meal)

Table 2 The classification of stomatitis at Kashiwa City Hospital

Grade	Grade description
1	Erythema of the mucosa
1.5	Erythema of the mucosa and pain from stimulation by foods
2	Patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)
2.5	Patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous) and mucosal pain caused by all foods (eating and deglutition are possible)
3	Confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)
3.5	Confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter, there is continuous pain, but water intake is possible)
4	Necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
4.5	Always bleeding, have pain and cannot sleep, and water intake is not possible.
5	Death related to toxicity

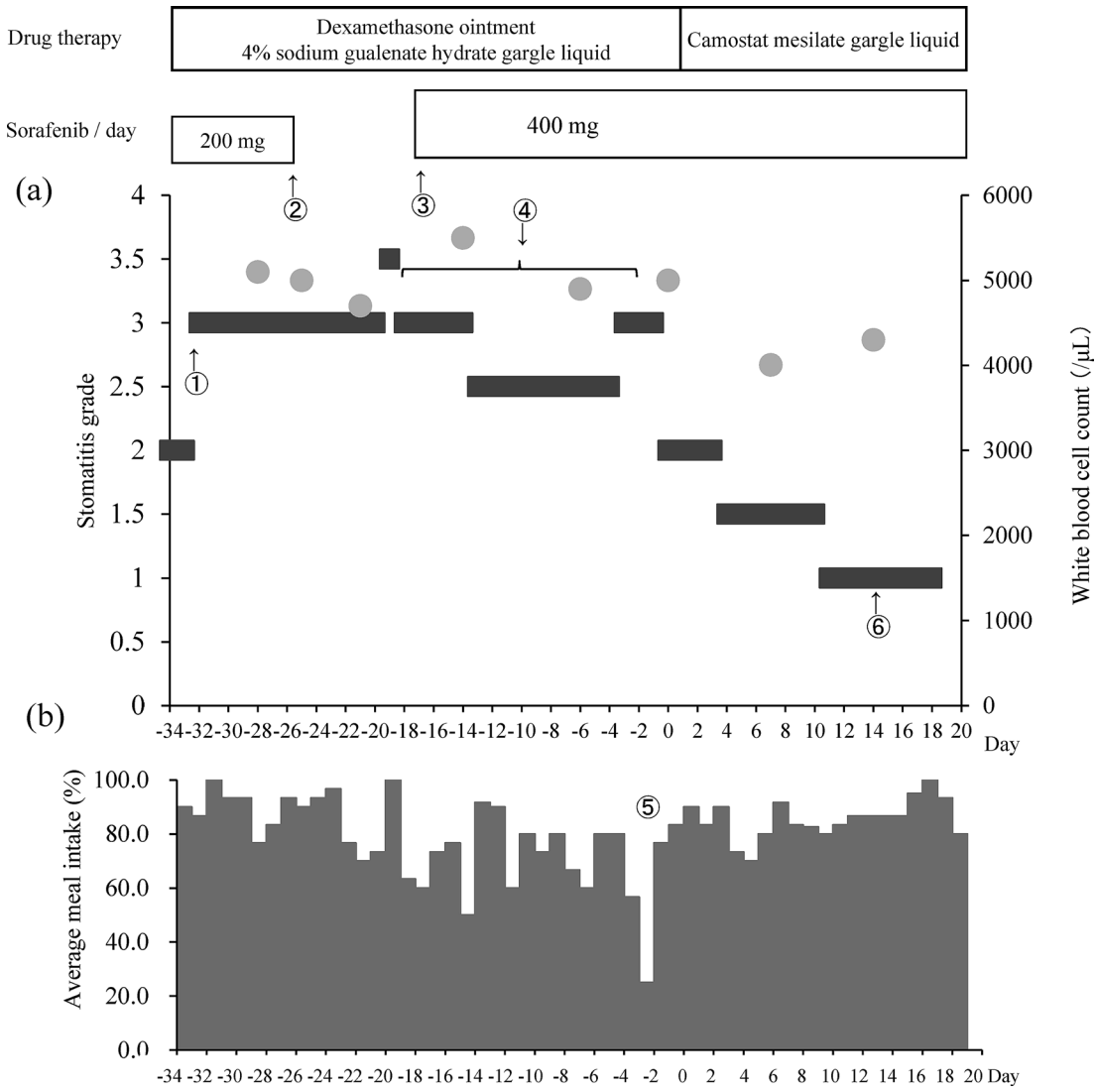

Fig. 1 The timeline of treatment with camostat mesilate gargle. (a) Changes in the neutrophil count and stomatitis grade, ● : White blood-cell count, ■ : Stomatitis grade. (b) Ratio of the average meal intake.

Table 3 Preparation of the camostat mesilate gargle

Preparation	①Camostat mesilate tablet	1,000 mg
	Carboxymethylcellulose sodium	5 g
	Simple syrup	50 ml
	Distilled water	add 500 ml
	②Sodium hydrogen carbonate	10 g
	Distilled water	add 500 ml
Storage	Store in a cool and dark place	
Usage	Six times per day: 1. Take 20 ml into mouth; spit it out five minutes later. 2. Then, 15 min later, take 20 ml into mouth and spit it out once again.	

CMG. The patient had difficulty eating because of tongue pain, but she had an appetite (Fig. 1-⑤). Her average meal intake rates had decreased by about 40%. Two days before starting CMG, the patient's diet was changed to rice porridge and soft vegetables. The patient's C-reactive protein (CRP) value was 6.8 mg/dl, and the patient showed evidence of inflammation. The white blood cell count was 5,000 /μl, a decrease from the time of admission. The patient was eager for stomatitis treatment, and started using CMG six times a day according to her dosing schedule at 11:00 am, 1:00 pm, 3:00 pm, 5:00 pm, 6:00 pm, and 9:00 pm. When the patient could not gargle, the frequency was reduced to three times a day. The patient was able to eat from the first day after starting CMG, and the stomatitis started showing improvement on the second day. On the third day, the stomatitis had decreased at

many points of the tongue. The stomatitis became a small spot, and the number of spots decreased. The spots continued to decrease on the fifth day after treatment was started. Then, 7 days after starting CMG, the spots on the tongue decreased sharply, and the color of the tongue returned to normal from a reddish tinge. The stomatitis decreased to Grade 1.5. At 7 days after starting CMG (and the third week since sorafenib had been increased to 400 mg/day), the tumor was smaller, and the white blood cell count had decreased to 4,005 /μl. The white blood cell count reached its lowest level on this day, but the stomatitis remained at Grade 1.5, and the CRP value had decreased to 5.5 mg/dl. However, there was no change in the patient's general condition, such as liver function, and serious stomatitis was not seen again. Therefore, sorafenib was continued. Ten days after starting CMG, most of the white inflammation of the tongue had disappeared, and the surface of the tongue became smooth. Eleven days after starting CMG, the stomatitis became Grade 1, and the patient could eat about 85% of a meal. Fourteen days after starting CMG, the tongue pain, stinging feeling, and an intraoral ulcer had almost completely disappeared, and the inflammation was improved (Fig. 1-⑥). The patient was careful with respect to the side effects of sorafenib and decided to continue treatment as an outpatient. When the patient showed signs of stomatitis, her dietary intake was considerably decreased. When she had Grade 3 stomatitis, she was not able to take in 1,600 kcal/day and ate only soft gel-like foods. However, the stomatitis improved after CMG was started, and meal intake increased. The weight loss experienced by the patient was limited to 5 kg, and her weight never fell below the standard body weight of 46.3 kg.

DISCUSSION

It is said that approximately 40% of cancer patients treated with chemotherapy develop stomatitis[14]. Molecular targeted drugs have many specific side effects previously unknown and sometimes unpredictable, different from those seen in conventional anticancer agents.

It has been reported that stomatitis accounts for 8% of the side effects of sorafenib administration for the treatment of renal cell and hepatocellular carcinomas[15]. Furthermore, it has been reported that the stomatitis is serious in 0.4% of cases[15]. In the present case, the patient had side effects, such as hypertension, a hand-foot skin reaction, and myeloablation, which are commonly induced by chemotherapy. In particular, the present patient also developed severe stomatitis, which is reported as a side effect caused by a molecular target agent[4]. Furthermore, since the patient in this case developed the stomatitis in the early period, it is considered that the stomatitis observed in this case was due to sorafenib.

In the present case, though steroid ointment and a mouthwash containing sodium gualenate hydrate were prescribed for an episode of stomatitis, they were not effective. Furthermore, although rebamipide, which has been described as effective for stomatitis, was orally administered, the onset of stomatitis could not be prevented in this case.

Stomatitis caused by anticancer agents can be prevented and treated effectively when the free radicals generated by the anticancer agents are controlled[16]. It has been reported that camostat mesilate at clinical doses is ineffective against free radicals[16]. On the other hand, Yosano and others reported that camostat mesilate gargle was effective against stomatitis caused by the combination of tegafur, gimeracil and oteracil potassium (TS-1)[11].

The white blood cell count was monitored in this case, since myeloablation is a known side effect of sorafenib. In this case, immediately before starting CMG, the dose of sorafenib was increased to 400 mg/day from 200 mg/day. Because the white blood cell counts decrease, an infectious disease may be caused by the myeloablation caused by sorafenib. As a result, it is thought that the stomatitis becomes more severe. Therefore, the white blood cell count was carefully monitored.

At that time, the stomatitis was Grade 3, showing ulcers with extensive erythema, and the patient could not swallow food. Furthermore, the white blood cell count of the patient decreased with increasing dosage of sorafenib, falling to half of the level measured at the time of hospitalization. At that time, the stomatitis was at its worst. With the use of CMG, the white ulcers affecting part of the patient's tongue and mouth disappeared almost immediately; she was then relieved of the pain and fear of biting and was able to eat more. In this case, the use of CMG was considered appropriate to relieve the patient's stomatitis.

As a result of the CMG treatment, stopping sorafenib target therapy due to aggravation of stomatitis could be avoided. The stomatitis did not worsen with the decrease of the white blood cell count after CMG treatment was started. In this case, infection caused by the white blood cell count decrease was not observed. However, though the relevance of this is unclear, the relationship between the white blood cell count and stomatitis needs to be examined in future studies.

From the above, CMG appears effective for stomatitis caused by the molecular target medicine sorafenib. However, CMG requires gargling six times a day to increase drug contact with the oral mucosa. It is also necessary to gargle with sodium bicarbonate water after gargling with CMG to remove the bitterness of CMG from the mouth; this can cause a substantial burden to patients.

In the future, we will study methods of masking the bitterness of CMG and increasing exposure of the oral mucosa to CMG.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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