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Multidisciplinary approach to the management of capecitabine-associated hand foot syndrome in cancer patients receiving capecitabine plus oxaliplatin and bevacizumab for advanced colorectal cancer

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Abstract

Objectives: To evaluate the management of adverse reactions in patients receiving initial capecitabine plus oxaliplatin (CapeOX) and bevacizumab (BV) therapy by a team consisting of doctors, pharmacists, and a nurse.

Methods: The study included 30 patients with advanced recurrent colorectal cancer whose initial therapy was CapeOX + BV. Each member of the multidisciplinary team had predefined tasks. The team held meetings weekly to decide on measures to be taken against adverse reactions at the upcoming outpatient visit. At these meetings, the nurse provided information obtained by weekly telephone support. Treatment outcomes and the incidence of adverse reactions were examined. Additionally, the effectiveness of telephone support provided by the nurse in terms of patient satisfaction was evaluated by questionnaire.

Results: The response and disease control rates were 66.7% and 96.7%, respectively. Grade 2 hand-foot syndrome occurred in 10.0% of the patients, none of these reactions being Grade 3 or greater. All patients were satisfied with telephone support.

Conclusions: Team management of adverse reactions in patients receiving CapeOX + BV therapy resulted in increased disease control rates and reduced the incidence of adverse events compared with a control group. Telephone support provided by the nurse contributed to improved patient satisfaction and provision of additional information to healthcare professionals.

Keywords: CapeOX, Team management, Telephone support, Hand-foot syndrome, Colorectal cancer

Introduction

The use of capecitabine plus oxaliplatin (CapeOX) therapy, a standard treatment regimen for advanced recurrent colorectal cancer, has some advantages, including no need for port placement and long intervals between hospital visits. However, adverse reactions such as hand-foot syndrome (HFS) and diarrhea need to be monitored and good drug compliance depends solely on the patients.[1] Although HFS caused by capecitabine may necessitate discontinuation of treatment, the efficacy of Cotaryl cream (urea/lactic acid; FDC, Bihar, India) for the treatment of HFS has been examined.[2] Thus, completion of this therapy requires patient education and supportive care by medical staff. Since September 2009, a team of doctors, pharmacists, and a nurse has provided support, including telephone support, to patients receiving CapeOX therapy from our institution. In this observational study, we studied the treatment outcomes, incidence of adverse events and effects associated with this approach.

Methods

Between November 2009 and April 2011, 30 patients (21 men and nine women) who received CapeOX (oxaliplatin [L-OHP] 130mg/m^2 on day1 in combination with capecitabine 2,000 mg/m^2/day on days1–14 at 3 weekly intervals) as initial treatment for advanced recurrent colorectal cancer were enrolled in this prospective study. Relevant patient and tumor characteristics are shown in Table 1. A team of doctors, pharmacists, and a nurse was involved in the management of adverse reactions. The need for prescribing moisturizing ointment (urea/lactic acid-based) or steroids to treat HFS was assessed, and drug compliance and the incidence of adverse reactions determined via telephone support.

Roles of the doctors

The doctors obtained informed consent for participation in the study from the patients and introduced the team members to them. At outpatient visits, the doctors assessed the severity of myelosuppression and presence of disease progression, and determined the grade of HFS based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Roles of the nurse

Before initiation of chemotherapy, the nurse provided treatment details to the patients and their families, including giving them a pamphlet, and demonstrated how ointment should be applied to the hands and feet three to five times a day. They also instructed patients and their partners on how to use gloves and cosmetics and obtained the details of the patients' employment and activities of daily living of before the initial administration of drugs. At every outpatient visit, the nurse interviewed the patients regarding symptoms of peripheral neuropathy and HFS and instructed them on

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moisturizer application. The nurse also took photos of the patient's hands and feet for assessment of the grade of HFS. In particular, because they were often inadequately examined by the doctors, the nurse carefully examined the patients' feet. The patients were telephoned weekly to determine the current grade of HFS based on CTCAE version 3; enquire about appetite, diarrhea, other evidence of gastrointestinal disorders, and other adverse reactions and given simple instructions. If emergency treatment was required, the nurse advised the patient to visit the hospital for assessment by the doctors.

Table 1. Patient characteristics (n=30)

	CapeOX (n=30)	
	No. of patients	%
Sex		
male	21	70
female	9	30
Age, mean (range)	64.3 (37-76)	
ECOG PS		
0	12	60
1	8	40
Primary tumor location		
colon	18	60
rectum	12	40
Metastatic site		
liver	16	53.3
lung	11	36.7
lymph node	8	26.7
others	5	16.7
No. of metastatic sites		
1	15	50
2	10	33.3
3	3	10
>3	2	6.7
Adjuvant chemotherapy		
yes	9	30
no	21	70

CapeOX, capecitabine plus oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group performance status

Roles of the pharmacists

Before initiation of chemotherapy, the pharmacists explained the treatment schedule to the patients and their families, including giving them using a pamphlet. To monitor compliance for capecitabine, the pharmacists distributed diaries and explained how to enter the required data. At every outpatient visit, the pharmacists checked the diaries to assess whether the patients had HFS or gastrointestinal disorders. To prevent progression of HFS, especially to Grade 2, the pharmacists recommended early use of various strengths of steroids if the patient had developed tingling and painless erythema of their hand and foot skin.

The members of the three professions held meetings weekly to share information, including that obtained via the nurses' telephone support and the pharmacists' rounds. Furthermore, the grade of HFS was assessed by all members of the team by reviewing the pictures taken by the nurse. On the basis of this information, the team members predicted when adverse reactions might occur and decided on the best treatment to provide at the next outpatient visit.

Efficacy of chemotherapy was assessed according to the Response Evaluation Criteria in Solid Tumors. Dose intensity was calculated for four, six, and eight courses of therapy. A questionnaire on the telephone support provided by the nurse was administered at the end of the study.

Results

Four of the 30 patients (13.3%) found it difficult to continue treatment, one because of development of Grade 3 diarrhea immediately after the initial dose, one because of Grade 2 HFS, and two because of malaise. The doses were reduced in 12 patients (40.0%), five of whom (16.7%) underwent dose reduction twice.

Overall assessment

Complete responses were observed in three patients (10%), partial responses in 17 (56.7%), no change in five (16.7%), and progressive disease in one (3.3%). The overall response rate was 66.7% and the disease control rate 96.7%. Mean progression-free survival (PFS) was 11.7 months.

Adverse events

HFS occurred in 23 patients (76.7%), 20 of whom had Grade 1 HFS (66.7%) and three Grade 2 HFS (10.0%). None of the patients had Grade 3 or greater HFS. Grade 2 and Grade 3 diarrhea each occurred in four patients (13.3%); however, this was controlled in many patients by withdrawing or reducing cathartics and/or antiflatulents or adding antidiarrheal drugs. Myelosuppression was observed in one patient in the form of Grade 2 thrombocytopenia, for which the doses of both capecitabine and oxaliplatin (L-OHP) were reduced by one step. Grade 3 peripheral neuropathy developed in three patients (10.0%). All of these adverse events occurred after seven courses. The adverse events are summarized in Table 2.

Table 2. Frequency of adverse events

	CapeOX (n=30)			
	All grades		Grade 3-4	
	N	%	N	%
Hand-foot syndrome	23	76.7	0	0
Peripheral neuropathy	19	63.3	3	16
Diarrhea	20	66.7	4	13.3
Nausea and vomiting	15	50	1	3
Neutropenia	5	16.7	0	0
Thrombocytopenia	5	16.7	0	0
Fatigue	21	70	1	3
Hypertension	7	23.3	0	0
Perforation	1	3	1	3
Proteinuria	8	26.7	0	0

CapeOX, capecitabine plus oxaliplatin

HFS and care

The grade of HFS tended to increase in parallel with the number of therapy courses, dry skin and deformed nails being the commonest manifestations. The frequency of application of moisturizer to the hands and feet (from three to four times per day for the hands and approximately twice a day for the feet at the start of treatment) gradually decreased because HFS did not occur in the early phase. However, the frequency of application increased when symptoms appeared at around

the fifth course. Male patients tended to apply moisturizer less frequently than female patients. However, after receiving instructions and experiencing HFS, the male patients applied moisturizer as frequently as did the female patients (Figure 1).

By the end of eight courses, the mean amount of moisturizer prescribed to the enrolled patients was 1.2 tubes per week, each tube containing 25 g moisturizer. In contrast, the mean amount of prescribed moisturizer in 11 patients who did not receive support during the same period was 0.4 tubes per week.

Dose intensity

The relative dose intensity of capecitabine was 91.2% for four courses, 91.0% for six courses, and 83.3% for eight courses. That of L-OHP was 92.4%, 89.2%, and 66.6%, respectively.

Survey on satisfaction with telephone support

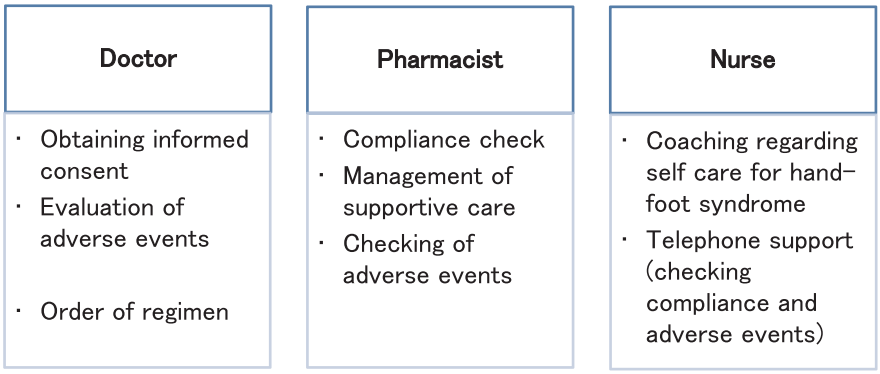
Responses to a survey on satisfaction were obtained from 24 patients at the completion of the study. All of them reported that they were very satisfied with receiving telephone support (Table 3).

Discussion

While CapeOX therapy, one of the standard regimen for advanced recurrent colorectal cancer, is reportedly as effective as FOLFOX chemotherapy (folinic acid, L-OHP, and 5-fluorouracil), the former has some advantages, including no need for port placement and long intervals between hospital visits.[1,3] However, adverse events such as HFS and diarrhea caused by capecitabine often affect treatment continuation. The incidence of Grade 2 or greater HFS, which adversely affects daily life, was approximately 15% in the 16967 study.[3] Although the incidence of Grade 3 or greater HFS was 6% in the 16966 study [4,5], 21% of patients had difficulty continuing treatment CapeOX therapy because of adverse events. However, the incidence of myelosuppression was reportedly lower with this therapy than with FOLFOX chemotherapy. Whether CapeOX therapy was continued or not appeared to have been determined by the development of adverse reactions, which are easily perceivable by patients. We therefore conducted an observational study in patients receiving CapeOX therapy to assess the efficacy of management of HFS by a team of three professionals. In this study, the incidences of Grade 2 and 3 adverse events were 10% and 0%, respectively, which are lower than in previous studies. Treatment continuation was difficult in 3.3% of the patients because of HFS and in 6.6% because of diarrhea. These rates are also lower than those previously reported. The dose intensity for eight courses was 83.3%, indicating that sufficient doses had been administered. Although the multidisciplinary team management of adverse events appears to have contributed to these results, it is difficult to determine what aspect of this approach contributed to the favorable results.

Reduction of capecitabine dose reportedly does not affect

Figure 1.



Role of the team members

Table 3. Questionnaire survey on satisfaction concerning telephone support

	Questionnaire	Responses (24 of 30 patients)
1	Content of telephone support	Very good (24)
2	Interval between telephone calls	Very good (24)
3	Length of telephone call	Very good (24)
4	Day and time of telephone call	Very good (13); Good (10); Fair (1)
5	Burden associated with telephone calls	Nothing (24)
6	Strictness of person in charge	None (18); Good (5); Fair (1)
7	Adequacy of coaching	Very good (14); Good (8); Fair (2)
8	Desire for telephone support after this study	Strong hope (22); Hope (2)

Figure 2.

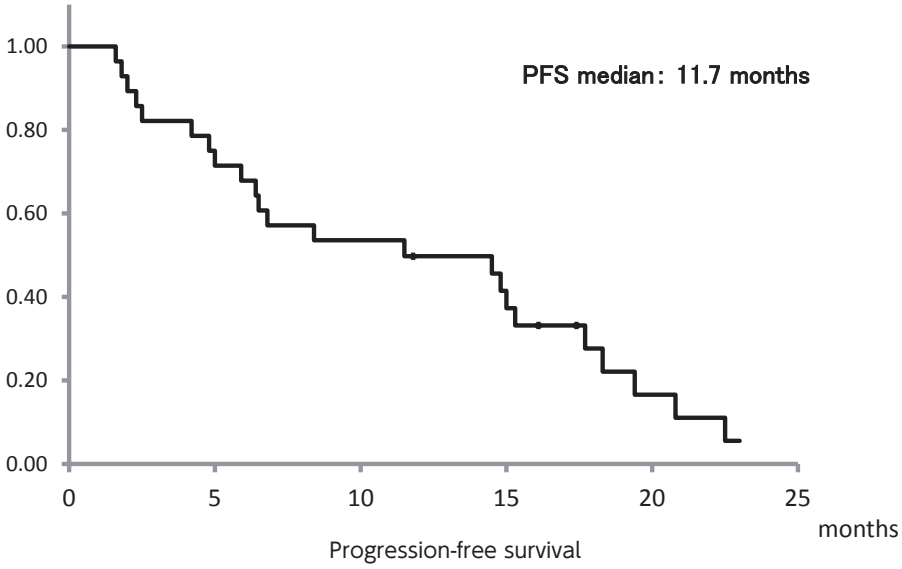
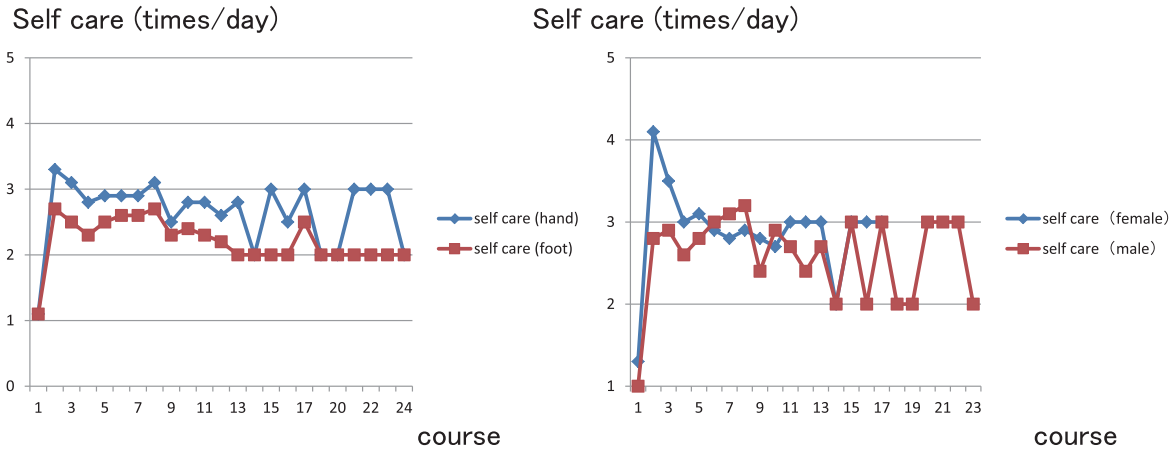


Figure 3.



self care frequency according to body part(left panel) and gender (right panel)

therapeutic outcomes.[3] Mean PFS was 11.7 months in our study, which compares well with that previously reported. In the Bevacizumab Expanded Access Trial study, the PFS was 10.8 months[1,3] There is no established method for preventing or treating HFS. In the present study, the patients were taught to apply the appropriate amount of moisturizer in the correct way. The pharmacists also taught the patients to use steroids earlier. Activities of daily living and the usage of moisturizers were assessed and checked by telephone support. In some cases, the nurse recommended early discontinuation of drugs. Although the HFS symptoms intensified in parallel with the number of courses, the practice of skin care appeared to have been almost established by the fourth course. Therefore, this did not differ between male and female patients. The patients were very satisfied with the telephone support, many of them requesting continuation after completion of the study. Patients who participated in the present study had more moisturizer prescribed than those who were not in the study, which suggests that patients do not adequately care for themselves when they only receive verbal instructions from their doctors. We therefore conclude that specific instruction on the use of moisturizers facilitates patients to adequately care for themselves.

Previous studies conducted in other countries have also shown favorable results for telephone support.[6-10] The number of communication skill training sessions reportedly affects patients' anxiety and coping strategies.[11] Some patients likely appreciated telephone support because they were very anxious, especially in the early phase of treatment. However, an objective assessment of the patients' health-related quality of life is needed to verify this possibility. In the present study, the patients were coached by one nurse and three pharmacists and it seems likely that their coaching methods were reproducible; however, we have no evidence that they were. The coaching skills of healthcare professionals have to be reproducible for coaching standardization. Murugan et al. reported that a structured teaching program for self-management of HFS was effective [12].Whether the results of the present study can be reproduced in other multicenter studies has yet to be determined. Further studies are therefore necessary.

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