原 著

Telephone support for capecitabine management in Japanese colorectal cancer patients

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Summary

Aim: Oral chemotherapy regimens of capecitabine plus oxaliplatin (XELOX/CapeOX) are preferable to continuous administration of intravenous 5-fluorouracil/folinic acid and oxaliplatin (FOLFOX), and are widely favored by colorectal cancer (CRC) patients for convenience and flexibility. However, these therapies have a number of inherent disadvantages, including compliance requirements and delayed discovery of severe adverse events (SAEs) such as neutropenia and hand-foot skin reaction (HFSR). So we designed a single-institutional prospective observational study to evaluate whether telephone intervention was useful in reducing the incidence of HFSR among Japanese outpatients with metastatic CRC (MCRC) who were undergoing oral chemotherapy involving the use of capecitabine.

Methods: The subjects were CRC patients aged over 20 years who were undergoing oral chemotherapy involving the use of capecitabine. Eligible patients received periodic telephone intervention at 8, 15, 22, 29, 36 and 43 days after the treatment started. The primary endpoint was the incidence rate of grade 3 HFSR during three cycles of capecitabine administration. Secondary endpoints included the premature withdrawal rate, the treatment interruption rate, time to recovery from HFSR after interruption, mean cumulative dose, mean treatment duration, compliance, and phone call duration.

Results: Between June 2010 and May 2012, a total of 20 eligible patients were enrolled. The incidence rate of grade 3 HFSR was 0%, and there was no withdrawal of administration due to HFSR. The average relative dose intensity of capecitabine was 94.3% (range: 75.0 - 101.6%).

Conclusion: Telephone intervention for Japanese CRC patients undergoing oral chemotherapy suppressed the incidence rate of severe HFSR.

Keywords : capecitabine, colorectal cancer, hand-foot skin reaction, oral chemotherapy, telephone support

INTRODUCTION

Combinations of 5-fluorouracil (FU)/folinic acid (FA) and either irinotecan (e.g., FOLFIRI) or oxaliplatin (e.g., FOLFOX) are established as forms of standard chemotherapy for the treatment of metastatic colorectal cancer (MCRC), and are widely used in Japan. Capecitabine (Xeloda; Hoffmann-La Roche Inc., Nutley, NJ) is an oral fluoropyrimidine with a level of efficacy similar to that of bolus 5-FU/FA both in first-line treatment of MCRC[1)-3)] and in adjuvant therapy for stage III CRC.[4)] Recently, the non-inferiority of XELOX (a regimen combining capecitabine and oxaliplatin) versus FOLFOX was demonstrated in two phase-III studies in first-line treatment of MCRC.[5), 6)] Oral chemotherapy involving the use of capecitabine has the advantage of eliminating the ports and pumps required for prolonged infusion of FU and avoiding complications associated with catheters. Accordingly, oral chemotherapy has been widely adopted in daily practice, and cancer patients tend to prefer it to intravenous therapy.[7), 8)]

However, severe adverse events (SAEs) caused by delays in intervention and poor adherence to medication schedules are major obstacles to the safe continuation of oral chemotherapy. It is also difficult to monitor outpatients, undergoing oral chemotherapy involving the use of capecitabine, who only visit a clinic or physician every three weeks in terms of maintaining compliance and minimizing toxicity.

Although various tools such as daily diary cards and leaflets may be useful in maintaining good

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compliance with medication schedules and detecting adverse events early, patient education and monitoring are even more important. Well-educated patients can understand and convey their condition effectively to medical staff. In this context, the approach of providing telephone support to monitor patients and to dispatch appropriate advice has been reported for antiretroviral therapy,[9), 10)] diffuse large B cell lymphoma,[11)] Type 1 diabetes,[12)] Type 2 diabetes,[13)] hypertension,[14)] breast cancer[15)] and ovarian cancer.[16)] Although telephone services have also been used in healthcare and psychotherapeutic settings to improve quality of life for cancer patients undergoing chemotherapy,[17)] no study has yet investigated whether telephone intervention is useful in preventing SAEs resulting from chemotherapy.

Particular focus was placed on whether the incidence rate of grade 3 HFSR was reduced by telephone intervention among CRC outpatients undergoing oral chemotherapy involving the use of capecitabine. As this was a preliminary study with a small sample size, no control group was used, nor were data analyzed from QOL metrics.

PATIENTS AND METHODS

Patients

CRC patients undergoing oral chemotherapy involving the use of capecitabine at Sapporo City General Hospital (SCGH) between June 2010 and May 2012 were recruited for the study. All of them fulfilled the following criteria: (i) histologically proven colorectal carcinoma; (ii) age over 20; (iii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score between 0 and 2; (iv) undergoing oral chemotherapy involving the use of capecitabine.

Patients with uncontrolled diarrhea, serious comorbidity or other conditions unsuitable for the investigation were excluded. The study was carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. Written informed consent was obtained from all patients participating in the study, and approval of the protocol was obtained from the Institutional Review Board at SCGH.

Treatment

XELOX treatment consisted of a 2-h 130 mg/m^2 intravenous infusion of oxaliplatin on the first day plus 1,000 mg/m^2 of oral capecitabine twice daily for two weeks on a three-week cycle. The first dose of capecitabine was given on the evening of the first day and the last on the morning of the fifteenth day. Bevacizumab at a dose of 7.5 mg/kg was administered via 30- to 90-min intravenous infusion before oxaliplatin on the first day of the three-week cycle.

Study design and telephone support

The aim of this study was to evaluate the effectiveness of phone support for the management of capecitabine treatment in SCGH colorectal cancer patients. The study protocol was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID UMIN000004429). Patients in the study received telephone calls from a registered expert nurse (author Hiromi Takaguchi) at 8, 15, 22, 29, 36 and 43

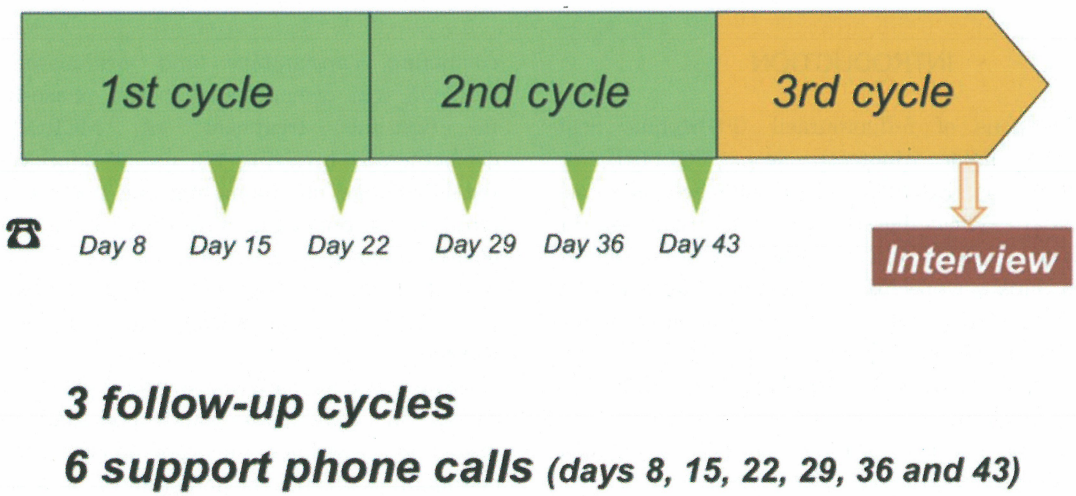

Figure 1. Telephone intervention
Telephone support services were done at baseline and at days 8, 15, 22, 29, 36 and 43 to assess the presence of severe HFSR or other problems. Participants were provided with the opportunity to ask questions regarding not only the treatment but also any severe problems they faced. At the end of three cycles of capecitabine treatment, a questionnaire survey was conducted.

days after the treatment started. After enrollment, the nurse met each patient to establish a telephone number, a convenient time for telephone support calls and passwords for proof of identify. In each of the support calls, the nurse used an interview template for guidance in asking whether the patients were experiencing SAEs or other problems. In addition, participants were provided with the opportunity to ask questions regarding not only the treatment but also any severe problems they faced. At the end of three cycles of capecitabine treatment, a questionnaire survey was conducted (Figure 1).

Outcome assessment

The primary endpoint of this observational study was to investigate incidence rates of grade 3 HFSR during three cycles of capecitabine. Evaluation for the presence of HFSR was assessed at baseline and at days 8, 15, 22, 29, 36 and 43. Secondary endpoints were the premature withdrawal rate, treatment interruption rates, time to recovery from HFSR after interruption, mean cumulative dose, mean treatment duration, compliance and phone call duration. All instances of toxicity including HFSR were graded according to the Common Terminology Criteria for Adverse Events (CTCAEs) version 3.0.[18]

Statistical analysis

Patient characteristics and study endpoints were summarized using descriptive statistics. The dose intensity of capecitabine was calculated by dividing the total dose by the number of weeks of treatment, and the relative dose intensity was calculated by expressing the total delivered dose of the agent per unit time (one week) as a percentage of the target dose.

RESULTS

Patient characteristics

The characteristics of the enrolled study patient population are shown in Table 1. From June 2010 to May 2012, a total of 20 patients were enrolled for the study (male: 9; female: 11; age range: 41 to 84 years; median age: 67 years). The ECOG performance status was 0 for fourteen patients, 1 for five patients and 2 for one patient, and the general condition of all patients was good. Among the subject group, 13 (65%) received XELOX plus bevacizumab, 6 (30%) received XELOX and 1 (5%) received capecitabine only.

Outcomes

Concerning AEs arising in response to oral chemo-

Table 1. Patient characteristics (n = 20)

Sex (%)	Male	9 (45%)
	Female	11 (55%)
Age (years)	median (range)	67 (41-84)
ECOG PS (%)	0	14 (70%)
	1	5 (25%)
	2	1 (5%)
Primary Site (%)	Colon	11 (55%)
	Rectum	9 (45%)
Resection of primary site (%)	No	10 (50%)
	Yes	10 (50%)
Metastatic / Recurrence (%)	Metastatic	17 (75%)
	Recurrence	3 (15%)
Metastatic site (%)	Liver	12 (60%)
	Lung	7 (35%)
	Lymph Node	8 (40%)
	Peritoneum	5 (25%)
	Spleen	1 (5%)
Clinical Lines (%)	1st line	16 (80%)
	2nd line	1 (5%)
	3rd line	3 (15%)
Regimens (%)	XELOX/BV	13 (65%)
	XELOX	6 (30%)
	capecitabine	1 (5%)

Abbreviations:
ECOG PS, Eastern Cooperative Oncology Group Performance Status
BV, Bevacizumab

therapy involving the use of capecitabine, grade 1 and 2 HFSR was recorded in 11 patients, but there were no cases of grade 3 (Tables 2, 3). Three patients (15%) were unable to continue treatment due to either progressive disease, hemorrhage or deteriorating PS, however none withdrew due to HFSR. Two patients (10%) needed to temporarily suspend treatment due to grade 1 diarrhea and grade 1 vomiting, respectively, with no capecitabine dose reduction. The median follow-up time was 331 days. The grade 3 AEs were hypertension (10%), thrombocytopenia (5%), fatigue (5%), and anorexia (5%), but none were life-threatening. Most AEs were grade 1 or 2 and could be controlled.

Table 2. Adverse events

	Number of patients						
Grade (CTCAE Ver 3.0)	1	2	3	4	5	Any Grade (%)	Grade 3/4/5 (%)
Neutropenia	3	1	0	0	0	4 (20%)	0 (0%)
Leukopenia	5	0	0	0	0	5 (25%)	0 (0%)
Anemia	4	2	0	0	0	6 (30%)	0 (0%)
Thrombocytopenia	3	1	1	0	0	5 (25%)	1 (5%)
Diarrhea	1	2	0	0	0	3 (15%)	0 (0%)
Constipation	6	1	0	0	0	7 (35%)	0 (0%)
Fatigue	11	1	1	0	0	13 (65%)	1 (5%)
Nausea	5	1	0	0	0	6 (30%)	0 (0%)
Vomiting	3	0	0	0	0	3 (15%)	0 (0%)
Anorexia	6	0	1	0	0	7 (35%)	1 (5%)
Dysgeusia	3	0	0	0	0	3 (15%)	0 (0%)
Mucositis oral cavity	1	1	0	0	0	2 (10%)	0 (0%)
Hand-Foot Skin Reaction	9	2	0	0	0	11 (55%)	0 (0%)
Hyperpigmentation	1	0	0	0	0	1 (5%)	0 (0%)
Neuropathy-sensory	18	1	0	0	0	19 (95%)	0 (0%)
Proteinuria	0	2	0	0	0	2 (10%)	0 (0%)
Hypertension	3	4	2	0	0	8 (40%)	2 (10%)
Hemorrhage	2	0	0	0	0	2 (10%)	0 (0%)
GI perforation	0	0	0	0	0	0 (0%)	0 (0%)

Table 3. Outcomes

Outcomes	(%)	n = 20
HFSR Grade 3>	0%	0/20
Premature withdrawal rate	15%	3/20
(due to HFSR)	(0%)	(0/20)
Treatment interruption rate	10%	2/20
(due to HFSR)	(0%)	(0/20)
Time to recovery of HFSR after interruption	-	0/20
Mean cumulative dose - capecitabine	114.615 g	
(1st - 3rd cycle)	(25.200 - 151.200)	
Mean treatment duration (range)	9.2 weeks (3.0 - 11.6)	
(1st - 3rd cycle)		
Average Relative Dose Intensity - capecitabine	94.3% (75 - 101.6%)	
(1st - 3rd cycle)		
Compliance : Completion rate of capecitabine	50%	
(1st - 3rd cycle : 100% RDI of capecitabine)		
Overall mean talk time	9.72 min	

Abbreviations: HFSR, hand-foot skin reaction; RDI, relative dose intensity

The mean cumulative dose of capecitabine during the three cycles was 114.615 g (range: 25.200 - 151.200 g) and the mean treatment duration was 9.2 weeks (range: 3.0 - 11.6 weeks). Although the completion rate of capecitabine treatment was only 50%, this result was affected by the patients' own trivial influences such as visit delays due to public holidays; in fact, the average relative dose intensity of capecitabine was 94.3% (range: 75 - 101.6%). The overall mean phone call duration was 9.72 minutes.

Benefits of telephone follow-up

At the end of the intervention period, questionnaires on satisfaction with the telephone support service were distributed and returned by 15 patients. Respondents answered questions on a scale from 0 (Not sure) to 5 (Strongly agree), and the answers are shown in Table 4. Although most patients were satisfied with the trial, some expressed dissatisfaction with the infrequency of calls. However, comments in the free-response section of the questionnaire mentioned a sense of safety, ease of understanding regarding treatment, and a feeling that they were free to ask questions.

DISCUSSION

The results of the study showed that telephone support was effective in restricting the incidence of grade 3 HFSR and may be useful for the management of capecitabine treatment among Japanese CRC patients. In particular, a very high relative dose intensity of capecitabine was maintained (94.3%; range: 75 - 101.6%), and telephone support was also found suitable for treatment compliance. The overall mean phone call duration was 9.72 minutes, which minimized the related burden both on patients and on medical staff. Although it is difficult to draw conclusions regarding any influence on survival or educational benefits due to the limited sample size, such inexpensive and easily implementable telephone support has the potential to reduce the risk of SAEs associated with oral chemotherapy and help to prolong the time prior to treatment failure.

Although oral chemotherapy involving the use of capecitabine against MCRC has been widely adopted in daily practice and become a popular choice for patients in recent years, a number of related considerations must be addressed. These include issues of compliance, adherence, the risk of medica-

Table 4. Post-support questionnaire results

Questionnaire (15 replies)	5 Agree strongly	4 Agree somewhat	3 Newtral	2 Disagree somewhat	1 Disagree strongly	0 Not sure
1. It was a pleasure to participate in the study.	11	4	0	0	0	0
2. The concept of the study was easy to understand.	11	3	0	0	0	0
3. I received phone calls as scheduled.	12	3	0	0	0	0
4. The questions asked during the regular phone calls were understandable.	13	2	0	0	0	0
5. I felt free to ask the expert nurse questions.	13	2	0	0	0	0
6. I felt secure speaking to the medical staff.	14	1	0	0	0	0
7. The medical staff spoke clearly and appropriately	14	1	0	0	0	0
8. The scheduled number of calls was appropriate.	9	3	1	2	0	0
9. I believe my privacy was adequately protected.	13	2	0	0	0	0
10. The study gave me a feeling of trust in medical staff.	11	3	0	0	0	0
11. I would like to participate in future studies of this kind.	12	1	2	0	0	0

tion administration error, monitoring limitations and exacerbation of AEs. With regard to HFSR (a typical AE of capecitabine treatment), XELOX was associated with a higher incidence of grade 3 HFSR than FOLFOX-4 (6% vs. 1%) in a NO16966 trial.[5] Furthermore, the overall incidence of HFSR with the use of XELOX in a Japanese MCRC population was reported to be 78%, which was higher than that in the XELOX plus bevacizumab arm of the NO16966 study (39%).[19] A Japanese CRC population treated with capecitabine may tend to suffer HFSR, and the management of the condition is important for such patients. This paper reports on a study regarding the effectiveness of telephone support for capecitabine users, and the approach may be applicable to a much wider scope of treatments. Nowadays, new molecular targeted drugs are used for various malignancies, and are mostly oral medications. These drugs are often associated with acneiform eruption and other distinctive AEs in addition to HFSR. Another important consideration is related outpatients monitoring to maintain safe and continuous treatment. Many attempts have been made to improve adherence, and various measurement methods for this purpose exist.[20] By way of example, patient self-reporting can be adopted as a way of simply and effectively measuring adherence.[21), 22] Educational intervention involving patients, their family members or both can also be effective in improving adherence.[23), 24] Electronic medication-monitoring devices further provide highly detailed information on patterns of medication-taking behavior, and mobile phone systems for patient monitoring have been reported following several trials.[25)-27] Each method has advantages and disadvantages, and none is considered a gold standard.[28), 29] Although some approaches may be appropriate for certain patients, most such applications are passive ways of communication for medical staff. While the concept of making telephone calls may seem old-fashioned in this day and age, the approach represents a direct and proactive method of ascertaining a patient's condition. The question of whether or not to seek the advice of medical personnel should not be left to the judgment of patients, and this active approach may be ideal for elderly people who may not fully understand their condition as well as for Japanese patients, who tend to be mild-mannered and hesitate to seek counsel. In addition, some information may be accessible only through direct contact, and older people tend to be more familiar with telephone communication. Proactive follow-up by telephone can also eliminate or mitigate patient anxiety, and also helps medical personnel to check patients' understanding of the treatment. No negative feedback was received from the questionnaire survey conducted in this study, and several respondents indicated that the support provided had encouraged them and given them an increased sense of security. Some reported having hesitated about giving permission to be contacted by telephone freely, but had subsequently felt positive about receiving regular phone calls from an expert nurse regarding their condition because it helped them to maintain a regular relationship with medical personnel. This suggests that a proactive approach based on phone calls from medical staff is useful in providing psychological support to outpatients.

In conclusion, proactive telephone support was effective in restricting severe HFSR among Japanese CRC patients undergoing capecitabine treatment. In addition, a high dose intensity of capecitabine was maintained and safe home-based medical care was provided via this method. Furthermore, an active approach with respect to future AEs suggested a possible beneficial effect as a psychological boost for outpatients. Although the potential QOL improvement and educational effects of the telephone support approach implemented in this study were not evaluated, further investigation in future trials may be warranted.

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