Community pharmacist–led telephone follow-up enabled close management of everolimus-induced adverse events in an outpatient with metastatic breast cancer

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Introduction

Everolimus has recently been approved for the treatment of metastatic estrogen receptor–positive breast cancer. The BOLERO-2 trial revealed the efficacy of everolimus and exemestane treatment for patients with metastatic breast cancer.¹ However, several severe adverse events were observed. In the BOLERO-2 study, 26% of patients discontinued treatment due to adverse events and 62% required dose reduction or interruption due to adverse events.² Many adverse events, such as stomatitis, rash, fatigue, diarrhea, nausea and peripheral edema, have been reported after treatment.³ Therefore, early detection and intervention of adverse events are needed to avoid discontinuation of this treatment.

In recent years, many oral anticancer agents, such as everolimus, have been developed. These drugs have been predominantly administered in an outpatient setting. Outpatients self-administer the treatment at home after collection from a community pharmacy. This precludes the ability to monitor adverse events daily, and early detection and intervention for adverse events is difficult. A telephone follow-up could be a valuable approach to monitoring adverse events.⁴ Here, we report the successful use of community pharmacist–led telephone follow-up for the management of adverse events in an outpatient treated with everolimus and exemestane. To our knowledge, no such report has been published in the literature.

Case report

A 66-year-old Japanese woman with systemic metastatic breast cancer received everolimus and exemestane therapy on an outpatient basis. She had previously been administered several endocrine therapies, followed by chemotherapy for 9 years. She had been living alone far from a community pharmacy or hospital. We began telephone follow-up after dispensing her prescription.

The patient's treatment course after initiation of everolimus and exemestane treatment is shown in Figure 1. Telephone follow-up was performed 13 times during treatment. The severity of nonhematological adverse events was evaluated using the numerical rating scale (NRS). Table 1 shows the blood biochemistry data before treatment initiation. After treatment initiation, there were no adverse events on day 3. On day 11, stomatitis was noted (NRS: 5) and at this point, her food intake was not influenced by the stomatitis. The pharmacist instructed the patient to gargle with glycerin, as prescribed by her physician. On day 15, telephone follow-up revealed that the patient was unable to orally intake solids (NRS: 9). We informed her physician about her condition and treatment was immediately stopped. Until recovery, she was closely monitored and supportive care was provided via telephone. She mentioned that she had a history of using sodium azulene sulfonate. Sodium

FIGURE 1 Treatment course after initiation of everolimus and exemestane treatment*

*There were 7 dispensing visits and 13 community pharmacist-led telephone follow-ups during treatment with everolimus and exemestane. Mucositis and peripheral edema were evaluated using a numerical rating scale. Collaboration with the physician made it possible to continue treatment for 85 days.

azulene sulfonate has been reported to be useful for stomatitis.⁵ Therefore, she was instructed to frequently gargle with it, together with glycerin. Steroid preparations have been shown to be useful for preventing mammalian target of rapamycin inhibitor-associated stomatitis.⁶ Therefore, she was instructed to use the over-the-counter drug triamcinolone acetonide topical (Trafal Direct; Daiichi Sankyo Healthcare Co., Ltd., Tokyo, Japan) for aphthous stomatitis. Further, we recommended using an over-the-counter vitamin B supplement (Chocola BB plus; Eisai Co., Ltd., Tokyo, Japan), although there was no evidence of the usefulness of vitamin B for mammalian target of rapamycin inhibitor-associated stomatitis. The NRS was 9 on day 16; however, the severity of stomatitis gradually decreased after day 17. The patient had lost around 7 kg of body weight, but on day 21, she was able to eat solids. On day 23, we informed her physician that her pain caused by stomatitis had disappeared (NRS: 1). The treatment was restarted at a

dose of 5 mg everolimus and 25 mg exemestane. The discontinuation period was 10 days and supportive care allowed early restart of the medication. After the restart of medication, there was no recurrence of serious stomatitis. However, peripheral edema gradually became serious. On day 57, we reported severe edema (NRS: 8) to her physician and treatment was stopped. After follow-up examination, medication was restarted. However, hepatic dysfunction was observed on day 85. The treatment of everolimus and exemestane was discontinued and the next chemotherapy regimen was started.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Discussion

Telephone follow-up is the most appropriate approach among all clinical follow-up approaches and is an effective means to extend medical follow-up in a patient's home. Several

TABLE 1 Blood biochemistry data before the initiation of everolimus and exemestane treatment

Variable	
AST	48 IU/L
ALT	28 IU/L
ALP	1141 IU/L
LDH	494 IU/L
γ-GTP	202 IU/L
Alb	31 g/L
Cre	60.1 μmol/L
BUN	5.5 mmol/L
WBC	$5.06 \times 10^3/\mu\text{L}$
RBC	$2.66 \times 10^6/\mu\text{L}$
PLT	$147 \times 10^3/\mu\text{L}$
Hb	70 g/L
CRP	74,100 μg/L
CEA	3.9 μg/L
CA15-3	50.2 kU/L
KL-6	2538 U/mL
Glu	5.7 mmol/L

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CA15-3, carbohydrate antigen 15-3; CEA, carcinoembryonic antigen; Cre, creatinine; CRP, C-reactive protein; Glu, glucose; γ-GTP, gamma-glutamyl transpeptidase; Hb, hemoglobin; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

reports have revealed that nurse-led telephone follow-up could improve medication adherence, patient satisfaction and clinical outcomes in some diseases.⁷⁻⁹ On the other hand, few reports have shown that community pharmacist-led telephone follow-up improves outcomes. Adverse events caused by anticancer agents result in poor medication adherence and low quality of life. Stomatitis has been shown to significantly reduce quality of life.¹⁰ The BOLERO-2 trial showed that the occurrence of stomatitis was higher in Asian patients than in non-Asian patients.¹¹ In a previous study, more than one-third of all stomatitis events (grade ≥ 2 according to the National

Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) were reported in the first 2 weeks, and 3 weeks were needed to reduce the condition to grade ≤ 1 in patients with grade ≥ 3 stomatitis.¹ Some patients were reported to have discontinued treatment.² Severe rash or pneumonitis has also been reported to occur. Therefore, it is necessary to pay sufficient attention to adverse events caused by everolimus after treatment initiation.

In our case, telephone follow-up with consideration of the characteristics of oral anticancer agents led to the early detection of severe adverse effects. Continuous evaluation using a simple NRS helped provide feedback to this patient's physician. Further, supportive care by the community pharmacist enabled early restart of medication. The medication schedule was complicated by dose interruptions and reductions; however, close telephone follow-up prevented the deterioration of adherence. Visceral metastases were shown to shorten progression-free survival.² In our case, the presence of liver metastases was recognized. However, the patient's treatment duration was extended to 3 months.

In this case, in-person pharmaceutical intervention was impossible. Continued pharmaceutical intervention can allow a deeper understanding of the adverse events in outpatients treated with oral anticancer agents.¹² Guidelines for outpatient cancer care by community pharmacists were recently published.¹³ In addition, various practice tools have been developed for the safe use of oral chemotherapeutics.¹⁴ Such guidelines and practice tools will aid in pharmaceutical interventions by community pharmacists. Furthermore, community pharmacist-family physician collaboration as part of the oncology team can increase the safety and efficacy of treatments for outpatients. Therefore, community pharmacist-led telephone follow-up can improve the treatment outcome and the adherence of outpatients treated with oral anticancer agents. Clinical trials are needed to clarify the effectiveness of community pharmacist-led telephone follow-up for improving patient outcomes.

In conclusion, we report the successful use of community pharmacist-led telephone follow-up for the management of adverse events associated with oral anticancer agents. ■

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