Oncology pharmacist contributions to treatment with oral anticancer agents in a Japanese community pharmacy setting

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Introduction

Outpatient cancer chemotherapy has increased in prevalence with the development of oral anticancer agents. A major advantage of outpatient oral chemotherapy is convenience; however, patients may eventually experience adverse drug reactions (ADRs) at home. Serious ADRs decrease the quality of life and can be dose-limiting.¹ A multidisciplinary approach to care has been successfully applied in oncology, but few safeguards have been adopted for outpatient oral chemotherapy.² Therefore, the role of community pharmacists in oral chemotherapy is becoming increasingly important.

Pharmaceutical treatment of ADRs as well as the verification of dosage and schedule during conventional dispensing is necessary to maintain the efficacy and safety of oral chemotherapy. Oncology pharmacist-physician collaboration can lead to the identification of a number of significant issues for patients prescribed oral chemotherapy, demonstrating the important role of oncology pharmacists in the hospital-based multidisciplinary team.³

There are few reports on active clinical intervention by community pharmacists in oral chemotherapy.⁴ Although guidelines for outpatient cancer care by community pharmacists have been published,⁵ implementing pharmaceutical care is difficult owing to the lack of patient information, time and staff in community pharmacy

settings. There are significant concerns associated with implementing oral chemotherapy services in community pharmacies.⁶ Continuous education on this therapy is required for community pharmacists,⁷ which could ensure adequate and safe use of this therapy. In this survey, we retrospectively evaluated the contributions of a certified oncology pharmacist to cancer patients treated with oral anticancer agents in Japanese community pharmacy settings.

Patients and methods

We conducted a retrospective survey to evaluate the impact of pharmaceutical care by oncology pharmacists. Outpatients treated with oral chemotherapy (except in combination with intravenous chemotherapy) and counselled by a Japanese Society of Pharmaceutical Health Care and Sciences (JSPHCS)-certified senior oncology pharmacist at Gifu Pharmaceutical University Pharmacy between July 2015 and June 2016 were included in this study. A certified pharmacist checked the dosage of oral anticancer agents, rest periods and treatment feasibility. The certified pharmacist met the following eligibility requirements: (1) a current, active license to practise pharmacy in Japan; (2) completion of 5 years of practice experience following pharmacist licensure, (3) completion of residency programs accredited by JSPHCS for 5 years, (4) submission of summaries of 50 intervention

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cases with cancer patients and (5) achievement of a passing score on the Certification Examination. In addition, advice about ADR management, medication guides related to supportive care and ADR monitoring were provided. Furthermore, pharmaceutical care suggestions regarding prescriptions for supportive care and dose modification or discontinuation were communicated to physicians via telephone, e-mail or facsimile as needed. Pharmacist-guided over-the-counter (OTC) medications, nutritional products and self-care were also implemented, while medical examinations were encouraged. We retrospectively investigated the following points from electronic records: the oral anticancer agents administered, number of patients counselled by the certified pharmacist, amount of counselling, number of telephone follow-ups, severity of ADRs according to the Common Terminology Criteria for Adverse Events (CTCAE) and any pharmaceutical care in collaboration with physicians. The outcome of this study was prevention of exacerbation of adverse events by pharmaceutical care. Institutional review board approval for this retrospective study was obtained from Gifu Pharmaceutical University.

Results

Patient characteristics and community pharmacist counselling

A community pharmacist encountered 84 patients (56 male, 28 female) treated with oral anticancer agents. The median age was 70 (range: 29-90). Twenty-one different oral anticancer agents were administered. There were 296 counselling sessions (including 34 telephone follow-ups) for 1 year. We divided the patients into 3 groups, based on the anticancer agents administered: antineoplastic antimetabolite group (group A; $n = 43$), molecular-targeted agent group (group M; $n = 17$) and hormonal agent group (group H; $n = 24$) (Table 1). The number of counselling sessions per group were 177, 88 and 31 in groups A, M and H, respectively. More counselling sessions per patient were performed in groups A and M than in group H. In groups A and M, 27 (62.8%) and 11 (64.7%) patients experienced ADRs, respectively. Various ADRs were observed in these 2 groups. Grade 3 or higher ADRs were observed in patients treated with tegafur/gimeracil/oteracil, tegafur/uracil and everolimus + exemestane. The cumulative total

number of patients with any grade ADR was 69 and 25 in groups A and M, respectively, indicating that one or more ADRs per patient occurred in these 2 groups. Conversely, ADRs were not observed in group H.

Twenty-five different ADRs were recognized by a certified pharmacist. The most commonly observed ADR was palmar-plantar erythrodysesthesia ($n = 13$). Gastrointestinal ADRs such as diarrhea, oral mucositis, anorexia and nausea were also frequently observed ($n = 43$). The ADRs were mostly nonhematological. Grade 3 or higher ADRs were as follows: palmar-plantar erythrodysesthesia ($n = 1$), nausea ($n = 1$), blurred vision ($n = 1$) and anemia ($n = 2$) caused by tegafur/gimeracil/oteracil; vertigo ($n = 1$) caused by tegafur/uracil; and mucositis ($n = 1$) and anemia ($n = 1$) caused by everolimus + exemestane.

Pharmaceutical care via telephone follow-up and community pharmacist-physician collaboration

Sixteen patients in this survey received telephone follow-up and/or community pharmacist-physician collaboration (Table 2). Considering the predilection for occurrence of ADRs, telephone follow-up was implemented in 14 cases, including 12 and 2 patients in groups A and M, respectively. Telephone follow-up was not implemented in group H because all the patients in group H had already been treated with hormonal agents for more than 3 months and no ADRs had been detected at the first counselling. The total number of telephone follow-ups was 21 and 13 in groups A and M, respectively. Frequent telephone follow-up was implemented for 2 patients who had grade 3 or higher ADRs induced by tegafur/gimeracil/oteracil or everolimus + exemestane. Along with telephone follow-up, community pharmacist-physician collaboration was performed. This collaborative approach ameliorated ADRs and enabled patients 1 and 2 to continue oral chemotherapy. Despite the telephone follow-up performed for patients 3 through 5, the intensification of ADR severity could not be prevented by the certified pharmacist. Consequently, severe or life-threatening ADRs occurred in these patients and they were hospitalized because of diarrhea, anemia or vertigo. For patients 6 through 14, monitoring of ADRs and confirmation of treatment feasibility were performed by telephone follow-up. Severe ADRs did not occur in these patients and the

TABLE 1 Oral anticancer agents associated with adverse drug reactions

Patient groups and oral anticancer agents received	Patients	No. of counselling sessions	No. of patients with ADRs (highest grade per patient)				Types of ADRs				Cumulative total patients with ADRs (highest grade per event)			
			Grade 1	Grade 2	Grade ≥3	All grades, n (%)	Grade 1	Grade 2	Grade ≥3	All grades	Grade 1	Grade 2	Grade ≥3	All grades
Group A (antineoplastic antimetabolites)	43	177	12	12	3	27 (62.8)					42	22	5	69
Tegafur/gimeracil/oteracil	24	118	10	4	3	17 (70.8)					33	12	5	50
Tegafur/uracil	7	20	0	1	1	2 (28.6)					3	1	1	5
Capecitabine	6	25	2	3	0	5 (83.3)					5	5	0	10
Tegafur/uracil + leucovorin	2	8	0	2	0	2 (100.0)					1	2	0	3
Trifluridine/tipiracil	2	4	0	1	0	1 (50.0)					0	2	0	2
Fludarabine	1	1	0	0	0	0 (0.0)					0	0	0	0
Hydroxyurea	1	1	0	0	0	0 (0.0)					0	0	0	0
Group M (molecular-targeted agents)	17	88	5	5	1	11 (64.7)					13	10	2	25
Sorafenib	3	7	2	0	0	2 (66.7)					3	0	0	3
Sunitinib	2	22	0	2	0	2 (100.0)					3	5	0	8
Everolimus + exemestane	1	18	0	0	1	1 (100.0)					0	2	2	4
Axitinib	1	3	0	0	0	0 (0.0)					0	0	0	0
Imatinib	4	17	3	1	0	4 (100.0)					6	1	0	7
Dasatinib	3	11	0	2	0	2 (66.7)					3	2	0	3
Nilotinib	3	10	0	0	0	0 (0.0)					0	0	0	0
Group H (hormonal agents)	24	31	0	0	0	0 (0.0)					0	0	0	0
Bicalutamide	8	9	0	0	0	0 (0.0)					0	0	0	0
Tamoxifen	5	8	0	0	0	0 (0.0)					0	0	0	0
Flutamide	5	8	0	0	0	0 (0.0)					0	0	0	0
Anastrozole	3	3	0	0	0	0 (0.0)					0	0	0	0
Enzalutamide	1	1	0	0	0	0 (0.0)					0	0	0	0
Chlormadinone	1	1	0	0	0	0 (0.0)					0	0	0	0
Exemestane	1	1	0	0	0	0 (0.0)					0	0	0	0

All values are expressed as numbers of patients except as noted. ADR, adverse drug reaction. Severity of ADRs was graded according to the Common Terminology Criteria for Adverse Events version 4.0.

TABLE 2 Patients receiving pharmaceutical care through telephone follow-up and collaboration with physicians

Patient	Oral anticancer agents	Highest grade of ADR	Telephone follow-up	Collaboration with physicians	Outcome
1	Tegafur/gimeracil/oteracil	3	Yes	Yes	Ameliorated ADRs
2	Everolimus + exemestane	4	Yes	Yes	Ameliorated ADRs
3	Tegafur/gimeracil/oteracil	4	Yes	No	Hospital admission
4	Tegafur/gimeracil/oteracil	4	Yes	No	Hospital admission
5	Tegafur/uracil	3	Yes	No	Hospital admission
6	Tegafur/gimeracil/oteracil	2	Yes	No	Treatment continuation
7	Tegafur/gimeracil/oteracil	2	Yes	No	Treatment continuation
8	Tegafur/gimeracil/oteracil	1	Yes	No	Treatment continuation
9	Tegafur/gimeracil/oteracil	1	Yes	No	Treatment continuation
10	Tegafur/gimeracil/oteracil	—	Yes	No	Treatment continuation
11	Capecitabine	2	Yes	No	Treatment continuation
12	Tegafur/uracil	2	Yes	No	Treatment continuation
13	Trifluridine/tipiracil	2	Yes	No	Treatment continuation
14	Axitinib	—	Yes	No	Treatment continuation
15	Tegafur/gimeracil/oteracil	2	No	Yes	Treatment continuation
16	Sunitinib	2	No	Yes	Treatment continuation

ADR, adverse drug reaction. Severity was graded according to the Common Terminology Criteria for Adverse Events version 4.0.

treatments were continued. Although telephone follow-up was not performed for patients 15 and 16, prescription suggestions for supportive care were communicated to physicians. These suggestions were accepted, which led to the continuation of treatment.

Discussion

Cancer patients expect better pharmaceutical care⁸ and minimization of the need for undesirable dose reduction or discontinuation. Maintaining the quality of life and improving clinical outcomes are important goals in outpatient oral chemotherapy. To achieve these goals, it is necessary for community pharmacists to detect the onset of ADRs as soon as possible and resolve clinical issues. This survey revealed that various ADRs occurring at home were recognized by a certified pharmacist in a community pharmacy. Many ADRs were observed in patients treated with capecitabine or sunitinib. These 2 agents were stratified in the high-risk category.⁹ Everolimus and pyrimidine fluoride-based drugs such as tegafur/gimeracil/oteracil also induced several ADRs, and pharmaceutical intervention is

recommended for patients treated with these agents.

In Japan, medical examination and prescription are always necessary before dispensing a treatment. The community pharmacist verifies the legality, safety and appropriateness of the prescription order and supplies medicines according to the prescription. If patients experience ADRs at home after treatment, they speak to their physicians at their next examination. The physician evaluates the ADRs and prescribes supportive care agents or performs dose reduction or discontinuation. It is difficult to prevent severe ADRs in oncological settings using the above workflow. To prevent severe ADRs and improve clinical outcomes, the presence of oncology pharmacists in community pharmacies alone is not sufficient and the creation of new strategies is necessary. Considering the common occurrence of ADRs, telephone follow-up and community pharmacist-physician collaboration seem to be an effective strategy.

Pharmacists in community settings are well suited to identify and resolve ADRs. Ensuring the proper use of both prescription and OTC

drugs is one of the basic responsibilities of pharmacists.¹⁰ To resolve ADRs induced by anticancer agents, specialized knowledge and active intervention are necessary. In hospital settings, telephone follow-up of oncology patients by clinical pharmacists helped to identify ADRs.¹¹ Similarly, follow-up by the community pharmacist helped to identify ADRs in the current survey. Furthermore, pharmaceutical care through telephone follow-up and collaboration with physicians made it possible to ameliorate ADRs and continue the therapy. While this type of follow-up is an effective strategy to improve clinical outcomes and to detect ADRs early, in several cases severe ADRs could not be prevented by telephone follow-up, leading to hospital admission. It is necessary to consider the appropriate timing and frequency when developing a telephone follow-up program.

There are many limitations to prescription order verification for safe oral chemotherapy by community pharmacists. But certified pharmacists have also indicated a number of potential clinically significant issues for patients receiving oral chemotherapy in the hospital setting, thereby demonstrating the role of pharmacists in the multidisciplinary team.^{3,12} Prescription contents need to be systematically checked by multiple medical staff in hospitals, as is performed for intravenous chemotherapy.¹³ In addition, to evaluate the appropriateness of prescription contents, it is crucial for community pharmacists to monitor ADRs and provide feedback to physicians regarding their severity. Currently, many oncology pharmacists participate in oral chemotherapy in hospitals.¹⁴ Collaborations among community pharmacists, physicians and oncology pharmacists will lead to safe medication and improved clinical outcomes.

In this survey, the sharing of grading number based on CTCAE among medical staff was useful. In a previous study, we evaluated ADRs using a numerical rating scale.¹⁵ ADRs assessed in community pharmacies are mainly nonhematological. Therefore, patient-reported outcomes such as numerical ratings or visual analog scales can better reflect the daily status.¹⁶ ADR

information was shared with physicians by telephone, email or facsimile. However, such communication tools can be inefficient, as information distribution occasionally becomes unidirectional. An information and communication technology-based system for sharing patient information will be necessary for an optimal multidisciplinary approach.

In this study, pharmaceutical care was provided by a certified oncology pharmacist. It may be difficult for community pharmacists to clearly understand rapidly evolving cancer chemotherapy. The important points regarding pharmaceutical care that were the focus in this study were the types of ADRs that led to decreased dose intensity, prediction of ADR and grading of ADR. Community pharmacists can acquire more knowledge on the above elements through education. An integrated approach combining knowledge acquisition, telephone follow-up, and collaboration among community pharmacists, physicians and oncology pharmacists can lead to the improvement of clinical outcome of oral cancer chemotherapy.

This study has a major limitation. The results of this study were derived from pharmaceutical care conducted by only one certified oncology pharmacist. To generalize the results, large-scale investigation involving regular community pharmacists will be necessary.

Conclusion

It is difficult to protect outpatients treated with oral chemotherapy from life-threatening or severe adverse events with traditional dispensing in community settings. For the safe use of oral anticancer agents, continued education of community pharmacists on cancer chemotherapy is certainly important. Furthermore, community pharmacist-led telephone follow-up programs and systematic collaborations among community pharmacists, physicians and oncology pharmacists are necessary for successful administration of oral chemotherapy. In future studies, we will evaluate the efficacy of telephone follow-up and collaborations among community pharmacists, physicians and oncology pharmacists on clinical outcomes. ■

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