Needs of chemotherapy regimen checks procedure: from the survey on chemotherapy regimen checks performed by pharmacists in hospitals other than designated cancer hospitals in Japan

Takahiro Ohta, PhD\textsuperscript{a,b}, Shinya Suzuki, PhD\textsuperscript{a,*}, Akira Shinohara, PhD\textsuperscript{a}, Yasukata Ohashi, MS\textsuperscript{b}, Daisuke Ueki, MSc\textsuperscript{d}, Daisuke Konuma, BS\textsuperscript{d}, Yasuaki Ryushima, BS\textsuperscript{a}, Ryoko Udagawa, MS\textsuperscript{f}, Toshikatsu Kawasaki, BS\textsuperscript{a}, Masakazu Yamaguchi, BS\textsuperscript{b,f}

Abstract

Introduction: Pharmacists perform regimen checks of physicians’ prescription orders in hospitals for providing appropriate chemotherapy. Details of these steps and procedures are confined to reports within individual facilities.

Methods: In July 2016, a questionnaire was sent to the 33 pharmacists of the total 33 National Hospital Organization hospitals that were not cancer hospitals in Japan to survey the items checked in regimen checks and to assess whether the regimen checks are performed for oral anticancer drugs (OACDs) and injected anticancer drugs (IACDs) according to prescription category. The questionnaires included items on characteristics of respondents and their facilities and the 7 items related to regimen checks.

Results: All facilities responded to the questionnaires, and 15 and 22 of the facilities performed chemotherapy regimen checks for OACDs and IACDs, respectively. Regimen checks for OACDs were performed for 80% (12/15) of internal and 27% (4/15) of external prescriptions for outpatient care and 93% (14/15) of prescriptions for inpatient care. Regimen checks for IACDs were performed for 91% (20/22) of prescriptions for outpatient care and 100% (22/22) of inpatient care.

Conclusions: The surveyed facilities differed in terms of items checked, suggesting that procedures of regimen checks followed protocols unique to each facility. It is vital to establish an adequate procedure to perform safe chemotherapy.

Keywords: cancer chemotherapy, chemotherapy regimen checks, Japan, prescription review

1. Introduction

Pursuant to the Cancer Control Act implemented in April 2007, the Basic Plan to Promote Cancer Control Programs was formulated in June 2007. The Plan emphasized further enforcement of radiotherapy, chemotherapy, and surgical therapy as the focus of challenges and training of medical staff who specialize in them. Prefectural plans were formulated to promote comprehensive and systematic cancer care. This resulted in the addition of fees for designated cancer hospitals, cancer boards, and hospital-based cancer registries in the FY 2010 Revision of Medical Fees. In the 2014 revisions, the term cancer patient counseling fees was changed to cancer patient instruction fees so that pharmacists can charge fees for explaining the side effects of antineoplastic agents. For example, Demachi et al\textsuperscript{[2]} reported that the presence of a pharmacist during the physician’s examination in outpatient care increased safety in chemotherapy and another study comparing patients administered S-1, the combination of tegafur, gimeracil, and oteracil potassium, for gastric cancer with and without pharmacists’ interventions reported that pharmacists’ intervention of adjuvant chemotherapy for gastric cancer of chemotherapy regimen increased the rate of patients who completed the treatment from 39.4% to 91.7%.\textsuperscript{[1]}

The major conventional roles of Japanese pharmacists in cancer care have comprised dispensing and preparation of anticancer drugs. However, as the number of patients who undergo chemotherapy increases, occasions requiring pharmacists to perform regimen checks of physicians’ prescription orders increases so that patients can undergo safe and effective chemotherapy.\textsuperscript{[4–6]} In Japan, this procedure of verifying the anticancer regimen before preparation is known as “regimen...
check,” and this procedure has been reported to effectively prevent fatal errors. Atsumi et al. reported that the internal management of the patients’ information of chemotherapy regimens via electronic systems generally contributed to medical safety. Suzuki et al. surveyed the items on the effects of the board certification system checked voluntarily in regimen checks by pharmacists working in designated cancer hospitals. In terms of foreign studies, Crandell et al. and Punke et al. found that in pharmacies’ reports within individual facilities, suggesting that pharmacists perform these tasks without clear guidelines in other countries as well. Defining regimen checks that pharmacists perform on physicians’ prescription orders shall promote further safety in chemotherapy.

2. Methods

2.1. Study design and sample selection

We conducted a retrospective observational study to clarify the practices associated with pharmacists’ chemotherapy regimen checks in general hospitals without cancer designated hospitals by surveying 33 of the 43 member institutions of the Kanto-shinetsu Region National Hospital Pharmacists Association in Japan (http://www.kansinyaku.jp/) that were not cancer hospitals designated by the Ministry of Health, Labour, and Welfare.

In July 2016, the explanation of this survey and a questionnaire on Google forms were emailed to all the 33 pharmacist members of the institutions to survey the items checked in regimen checks and to assess whether the regimen checks are performed for oral anticancer drugs (OACDs) and injected anticancer drugs (IACDs) according to prescription category. We collected the survey form as an online digital file document.

2.2. Survey questions

The questionnaires included items on characteristics of respondents and their facilities and the following 7 items related to regimen checks: whether regimen checks were performed for OACDs and IACDs in 2015, items checked in the regimen check, doses and intervals between doses that warranted doubt inquiries, number of staff involved in the regimen checks, whether the regimen checks are performed according to standardized protocol, timing for doubt inquiries, and sources of information used for the regimen checks.

2.3. Ethics approval

Ethical approval was waived by the institutional review board of national hospital organization hospitals and national center hospitals due to a questionnaire survey of pharmacy service, which did not contain patient data.

2.4. Data analysis

Descriptive statistics were used to examine the mean number and frequency. Statistical analysis was performed using chi square test. All calculations were performed using Microsoft Excel 2016 for Mac.

3. Results

The response rate was 100% (33/33), and 85% (28/33) of the responding facilities had 200 to 499 beds. Among these facilities, 6% (2/33) had a Japanese Society of Pharmaceutical Health Care and Sciences-certified Oncology Pharmacist on their staff. Fifteen of the surveyed facilities performed regimen checks for OACDs, and 22 performed them for IACDs (Table 1).

3.1. Rate of regimen checks and items for OACDs and IACDs according to prescription category

Regimen checks for oral chemotherapy were performed for 80% (12/15) of internal and 7% (4/15) of external prescriptions for outpatient care and for 93% (14/15) of prescriptions for inpatient care. Regardless of prescription category, >90% of facilities that performed regimen checks checked the dose and the dosing period, whereas <50% of facilities checked supportive treatments, urine tests, history of allergies, and medical history. Regimen checks for IACDs were performed for 95% (21/22) of prescriptions for outpatient care and for 100% (22/22) of prescriptions for inpatient care. Regardless of prescription category, >90% of facilities that performed regimen checks checked the dose, height, weight, body surface area, and regimen name, whereas <50% of facilities checked supportive treatments, urine tests, history of allergies, and medical history (Tables 1–3).

3.2. Doses and intervals between doses that warrant doubt inquiries

All facilities had internal standard dose criteria to decide whether to make a doubt inquiry for both OACDs and IACDs. However, the facilities had similar standards for doubt inquiries based on intervals between doses 7% (1/15) for OACDs and 32% (7/22) for IACDs (OACDs vs IACDs, P=0.068) (Table 3).

3.3. Number of pharmacists involved in regimen checks

On an average, 1.8 pharmacists were involved in the regimen check for OACDs. However, it was most commonly handled by
only 1 pharmacist, and this accounted for 47% (7/15) of institutions surveyed that performed checks for OACDs. Regimen checks for IACDs involved 2 pharmacists on average, although it was most commonly handled by only 1 pharmacist, and this accounted for 41% (9/22) of institutions surveyed that performed regimen checks for IACDs (Table 3).

### 3.4. Time for performing regimen checks

Regimen checks for OACDs were performed after entering the physician’s prescription order on the day before administration in 73% (11/15), on the day of administration in 67% (10/15), and after the date of administration in 13% (2/15) of the institutions. Regarding IACDs, regimen checks were performed after entering the physician’s prescription order on the day before administration in 82% (18/22), on the day of administration in 73% (16/22), and after the date of administration in 5% (1/22) of the institutions (Table 3).

### 3.5. Standardized protocol for regimen checks

In total, 47% (7/15) and 73% (16/22) of the institutions had a standardized hospital protocol in place for regimen checks performed for OACDs and IACDs, respectively (Table 2).

### 3.6. Sources of information used for regimen checks

Package inserts in 93% (14/15), technical books on chemotherapy in 73% (11/15), and guidelines in 73% (11/15) were used for regimen checks for OACDs. Package inserts in 95% (21/22), technical books on chemotherapy in 77% (17/22), and pharmaceuticals interview form in 77% (17/22) were used for regimen checks for IACDs (Table 3).

### 4. Discussion

The study population comprised pharmacy departments of 33 member facilities of the Kanto-shinetsu Region National Hospital Pharmacists Association in Japan (http://www.kansyuaku.jp/), except Ministry of Health, Labour, and Welfare designated cancer hospitals. To our knowledge, this is the first study to report on the results of multicenter questionnaire surveys on regimen checks performed by pharmacists. We found that regimen checks for OACDs involved pharmacists in a high percentage of internal inpatient prescriptions, but the rate of prescriptions that went without pharmacists’ intervention was higher for internal outpatient prescriptions than for other prescription categories. The survey revealed that regardless of prescription category, regimen checks are not performed on all prescriptions and the items checked in the regimen checks varied between surveyed facilities. Regimen checks are probably being omitted for some prescriptions owing to the following reasons: shortage of manpower in the pharmacy department of surveyed facilities and prescriptions that are ordered without a regimen application. However, there are safety concerns for patients who are being administered anticancer drugs that are being prepared without checking the prescription for such reasons, which warrant measures to improve the situation.

Recently, there has been an increase in the demand for OACDs in the backdrop of several social factors. Availability of chemotherapy drugs that do not necessarily require hospitalization is increasing in Japan and abroad, and this has spurred a debate on how they should be handled.[12] The results of the present survey demonstrated that regimen checks were being performed by pharmacists at an extremely low rate for external prescriptions for outpatient care, despite the crucial importance of performing regimen checks for managing adverse events that occur during the outpatient care period. There are several reasons that may explain this finding. First, pharmacist involvement in external prescriptions in Japan is limited by constraints in manpower, which increase the workload of individual pharmacists. Additionally, the lack of protocols for regimen checks performed by pharmacists has resulted in the practice of regimen checks that are left to the discretion of pharmacists in each facility and likely discrepancies in the quality of regimen checks as a consequence. In fact, regimen checks were performed at higher rates for IACDs than for OACDs irrespective of whether the prescription was for inpatient or outpatient care. In Japan, where
the separation of prescribing and dispensing is practiced, pharmacies within the insured medical system should take on the role of managing OACDs prescribed for outpatient care. However, pharmacists in insurance-covered pharmacies do not have sufficient knowledge in oncology or OACDs, which would make it difficult for them to perform regimen checks, and this continues to place a larger part of the role on hospital pharmacists.\[13\]

Pharmacists play a vital role in inspecting prescriptions for drugs, including anticancer drugs. Integration of clinical pharmacy services reported pharmacists checks of the eligibility, start of treatment, dose reduction and discontinuation criteria for anticancer drugs based on protocol prior to preparation of injectable anticancer drugs was useful for reducing drug wastage after preparation and the number of drug-related problems.\[14,15\]

Hamel et al\[16\] found that erroneous doses were prescribed in 61.8% of 10, 214 prescriptions related to pediatric tumors and that 47.4% of these prescriptions originated in data on patient height and weight that were not up-to-date. Schaefer et al\[17\] reported an 88% risk of interactions between antineoplastic drugs and concomitant drugs in their retrospective survey of 202 patients with hematological malignancies, highlighting the importance of checking for interactions with other drugs as well when pharmacists perform regimen checks for antineoplastic drugs. In the present survey, concomitant drugs were checked in only approximately 50% of regimen checks performed for IACDs, irrespective of the prescription category. Suzuki et al\[7\] reported that pharmacist intervention prevents prescription order errors in outpatient chemotherapy, more frequent pharmacist intervention for outpatient care is observed, and dispensing and administering drugs prescribed erroneously by physicians can be prevented by manual or electronic intervention of computerized provider order entry by the hospital pharmacist. However, the present survey revealed that as with OACDs, not all prescriptions underwent regimen checks and that the items checked in the regimen checks varied between surveyed facilities. Moreover, we found that only 6% of facilities had a Japanese Society of Pharmaceutical Health Care and Sciences-certified Oncology

### Table 3

Questionnaire items for OACDs and IACDs.

| Questions | OACDs (15) | IACDs (22) |
|-----------|-----------|-----------|
| Q. How much percentage of regimen checks in chemotherapy in inpatients? | N, % | N, % |
| 1. 100% | 10 (66) | 21 (95) |
| 2. ≥90% | 0 (0) | 1 (5) |
| 3. ≥80% | 1 (7) | 0 (0) |
| 4. ≥70% | 0 (0) | 0 (0) |
| 5. ≥60% | 1 (7) | 0 (0) |
| 6. ≤50% | 3 (20) | 0 (0) |
| Q. How much percentage of regimen checks in chemotherapy in outpatients? | N, % | N, % |
| 1. 100% | 8 (53) | 20 (91) |
| 2. ≥90% | 0 (0) | 0 (0) |
| 3. ≥80% | 0 (0) | 0 (0) |
| 4. ≥70% | 1 (7) | 0 (0) |
| 5. ≥60% | 0 (0) | 0 (0) |
| 6. ≤50% | 6 (40) | 2 (9) |
| Q. Do you have standard doubt inquiries to ask the prescribing doctor when you have questions about the dose of anticancer agents? | N, % | N, % |
| 1. Yes | 15 (100) | 22 (100) |
| 2. No | 0 (0) | 0 (0) |
| Q. Do you have standard doubt inquiries to ask the prescribing doctor when you have questions about the interval of anticancer agents? | N, % | N, % |
| 1. Yes | 1 (7) | 7 (32) |
| 2. No | 14 (93) | 15 (68) |
| Q. How many pharmacists’ participate in chemotherapy regimen checks? | N, % | N, % |
| 1. 1 | 7 (47) | 9 (40) |
| 2. 2 | 5 (33) | 7 (32) |
| 3. 3 | 2 (13) | 3 (14) |
| 4. 4 | 1 (7) | 3 (14) |
| Q. Do you have standard items about chemotherapy regimen checks in your hospital? | N, % | N, % |
| 1. Yes | 7 (47) | 16 (73) |
| 2. No | 8 (53) | 6 (27) |
| Q. What time do pharmacists perform regimen checks of chemotherapy in your hospital? (multiple answers permitted) | N, % | N, % |
| 1. Order to prescription before the administration day | 11 (73) | 18 (82) |
| 2. Order to prescription on the administration day | 10 (67) | 16 (73) |
| 3. Order to prescription after the administration day | 2 (13) | 1 (5) |
| Q. What type of tools or methods do you have in chemotherapy regimen check? (multiple answers permitted) | N, % | N, % |
| 1. Package insert | 14 (93) | 21 (95) |
| 2. Interview form* for chemotherapy | 10 (67) | 17 (77) |
| 3. Technical books for chemotherapy | 11 (73) | 17 (77) |
| 4. Guideline for chemotherapy | 11 (73) | 16 (73) |
| 5. Others | 2 (13) | 3 (14) |

IACDs = injected anticancer drugs, OACDs = oral anticancer drugs.

*Pharmaceutical interview forms are supplement package inserts. < Japan Pharmaceutical Manufacturers Association: Pharmaceutical Administration and Regulations in Japan: http://www.jpma.or.jp/english/parj/pdf/2015.pdf >
Pharmacists on their staff. A Certified Oncology Pharmacist in Japan is required to have 5 years of experience, have credits in permanent education training, pass a written examination, and write up 50 case reports. It is unknown whether this correlates to clinical competence as a pharmacist; however, a previous study has reported that the presence of individuals with this certification reduces the rates of administering inappropriate treatments.\[4\]

There are several limitations to this study. First, it is a survey of Japanese facilities and the findings cannot be generalized to hospitals in other countries, given the different roles allocated to hospital pharmacists and their numbers. In particular, the majority of hospital pharmacists engage in dispensing, preparation of anticancer drugs, and drug management and other technical or administrative tasks because of the lack of a pharmacy technician system. In the majority of developed countries, preparation is performed by a technician and pharmacists working in oncology are dedicated to inspecting prescriptions in clinical practice, and such highly specialized pharmacists may not need a list of items to be checked in a regimen check. Although the number of Certified Oncology Pharmacists is increasing in Japan, they are still in shortage, as we found from the present survey. This implies that pharmacists with less knowledge in medical care may need to run regimen checks and that there may be a discrepancy in the quality of regimen checks even if the same parameters are being checked. In fact, although medication package inserts were the most commonly used source of information for regimen checks, it is difficult to assess a chemotherapy regimen based on the package insert alone. Other specialized knowledge, such as recommended doses, intervals, supportive treatments such as antiemetics, and criteria of the most recent clinical observations on which it is determined whether to administer the drug, is required. We found that the frequency of regimen checks was much lower for OACDs than for IACDs. In addition, it would have been ideal to analyze the roles of pharmacists working in insurance-covered pharmacies. However, this was omitted from the survey owing to the difficulty of selecting pharmacies for samples because external prescriptions are not necessarily dispensed by insurance-covered pharmacies in geographic proximity of prescribing hospitals.

In the future, a similar survey should be conducted on oncology hospitals and items that are checked should be standardized according to tumor types and regimens. The time taken before and after regimen checks and the changes in the number of doubt inquiries should be assessed in a prospective study. In the goal of standardizing protocols for regimen checks, a consensus must be reached domestically toward a domestic protocols and regulations. It is important to clearly define and normalize regimen checks to provide rigorous regimen check guidelines for all pharmacists involved in chemotherapy, particularly for those currently working in facilities that do not routinely perform regimen checks in cancer therapy. It is desirable to establish the regimen checks guideline in Japan as well as a consensus in international societies such as the International Society of Oncology Pharmacy Practitioners and the European Society of Oncology Pharmacy, to which many international countries belong.

Author contributions
Contributions: S.S. and T.O. designed the study. T.O., S.S., A.S., Y.O., D.U., and D.K. analysed data and wrote the manuscript. D.U., Y.R., and R.U. collected data. T.K. and M.Y. helped review and revise the manuscript.

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