Article

Not peer-reviewed version

Cancer Chemotherapy-Related Regimen Checks Performed by Pharmacists of General Hospitals Other Than Cancer Treatment Collaborative Base Hospitals: A Multicenter, Prospective Survey

Daisuke Ueki , Shinya Suzuki * , Takahiro Ohta , Akira Shinohara , Yasukata Ohashi , Daisuke Konuma , Yasuaki Ryushima , Ryoko Udagawa , Hironori Motonaga , Masahiro Ieoka , Akihiro Taji , Yuuki Kogure , Mikako Hiraike , Miyuki Uoi , Kasuhiko Ino , Toshikatsu Kawasaki , Masakazu Yamaguchi

Posted Date: 1 November 2023

doi: 10.20944/preprints202311.0032.v1

Keywords: cancer chemotherapy; chemotherapy regimen checks; pharmacist intervention; hospital pharmacist

Article

Cancer Chemotherapy-Related Regimen Checks Performed by Pharmacists of General Hospitals Other than Cancer Treatment Collaborative Base Hospitals: A Multicenter, Prospective Survey

Daisuke Ueki [1], Shinya Suzuki [2,*], Takahiro Ohta [3], Akira Shinohara [2], Yasukata Ohashi [4], Daisuke Konuma [5], Yasuaki Ryushima [6], Ryoko Udagawa [7], Hironori Motoshige [8], Masahiro Ieoka [9], Akihiro Taji [10], Yuuki Kogure [11], Mikako Hiraike [12], Miyuki Uoi [13], Kazuhiko Ino [1], Toshikatsu Kawasaki [2] and Masakazu Yamaguchi [14]

[1] National Hospital Organization Tokyo National Hospital, Department of Pharmacy, Tokyo, Japan
[2] National Cancer Center Hospital East, Department of Pharmacy, Kashiwa, Japan
[3] National Hospital Organization Tokyo Medical Center, Department of Pharmacy, Tokyo, Japan
[4] National Center for Global Health and Medicine, Department of Pharmacy, Tokyo, Japan
[5] National Hospital Organization Chiba Medical Center, Department of Pharmacy, Chiba, Japan
[6] National Hospital Organization Saitama Hospital, Department of Pharmacy, Saitama, Japan
[7] National Cancer Center Hospital, Department of Pharmacy, Tokyo, Japan
[8] National Hospital Organization Hokkaido Medical Center, Department of Pharmacy, Hokkaido, Japan
[9] National Hospital Organization Hamada Medical Center, Department of Pharmacy, Shimane, Japan
[10] National Hospital Organization Osaka Minami Medical Center, Department of Pharmacy, Osaka, Japan
[11] National Hospital Organization Higashihiroshima Medical Center, Department of Pharmacy, Hiroshima, Japan
[12] National Hospital Organization Kumamoto Medical Center, Department of Pharmacy, Kumamoto, Japan
[13] National Hospital Organization Kyusyu Cancer Center, Department of Pharmacy, Fukuoka, Japan
[14] Cancer Institute Hospital, Department of Pharmacy, Tokyo, Japan
* Correspondence: ssuzuki@east.ncc.go.jp; Tel.: +81-04-7133-1111

Abstract: The aim of this prospective study was to examine the issues of these items to evaluate the possibility of their application to clinical practice. This prospective survey was performed on pharmacists of 14 hospitals. The number of confirmation items was 345 and 375 items in the control group and recommended item group, respectively. The mean time required for completing a regimen check (±standard deviation) was 4 minutes and 14 seconds (±1 minute and 50 seconds) and 6 minutes and 18 seconds (±1 minute and 7 seconds) in the control group and recommended item group, respectively. Among the recommended items, the mean number of items that pharmacists confirmed was 12.4 and 18.6 in the control and recommended items, respectively. The number of doubt inquiries was higher in the recommended item group than in the control group (41 vs. 27 cases). The number of doubt inquiries related to dosage, premedication, urinalysis, and a history of hepatitis B virus was higher in the recommended item group than in the control group. In the present study, we created 19 items that should be confirmed in regimen checks and examined the possibility of their application to clinical practice.

Keywords: cancer chemotherapy; chemotherapy regimen checks; pharmacist intervention; hospital pharmacist

1. Introduction

The remarkable progress and advancements in the field of cancer chemotherapy have led to significant improvements in the survival outcomes of patients with cancer. Although a wide variety of treatment options are now available through the release of molecular targeting drugs and other new ones, safe management of cancer chemotherapy persists as an issue requiring intervention

 doi:10.20944/preprints202311.0032.v1

(Mitchell et al. 2021; Sandrine et al. 2022). According to a Norwegian study—with 3557 participants—that examined medication errors, the percentage of dosing errors was 38% (Alma et al. 2021). Such errors in cancer chemotherapy cause life-threatening events; thus, several measures have been implemented in each institution (Brian et al. 2017; Raymond et al. 2012). To minimize dosing errors, guidelines for cancer chemotherapy regimens were released in 1998 (Kohler et al. 1998). In Japan, many institutions have used regimens to eliminate cancer-chemotherapy disparities. In addition to doses of anticancer drugs, regimens include several aspects, such as supportive medications and rest periods. Regimens largely contribute to ensuring medical safety and standardizing cancer chemotherapy. The use of regimens reduces dispensing errors (Jacobson et al. 2012). Ranchon et al. analyzed 91 dosing errors of anticancer agents and reported that 53% of the errors were identified as a result of a doubt inquiry, resulting in medication changes (Ranchon et al. 2013). These analyses indicated that confirming prescribed medications by persons other than physicians is essential.

Intervention by pharmacists in cancer chemotherapy orders by physicians prevents dosing errors (Diaz-Carrasco et al. 2007; Freeman et al. 2019; Hayashi et al. 2015). In Japan, such duties of the pharmacists are referred to as regimen checks (Suzuki et al. 2017). However, to the best of our knowledge, no study has defined the selection criteria for confirmation items of regimen checks. Therefore, a difference in the quality of medical resources and pharmacists' competence may affect the successful implementation of regimen checks. Regarding confirmation items of regimen checks, Suzuki et al. performed a study involving pharmacists of cancer-designated hospitals and voluntarily surveyed some of the items (Suzuki et al. 2016). Griffin et al. (2016) reported 57 systematic checks used for injections of anticancer drugs; however, they did not define the selection criteria for confirmation items. Using this background, Ohta et al. (2021) prepared and used a questionnaire to examine confirmation items recommended for regimen checks. The results yielded 19 recommended items, which comprised items that are commonly confirmed by pharmacists and those that the authors determined to be essential for regimen checks, regardless of the confirmation rate by pharmacists (Table 1).

Table 1. Nineteen confirmation recommended items.

	Items	Additional notes
1	Height	Confirm measurement date. (If there is an institution-specific rule, e.g., within the last several months, confirm whether the measurement is performed within that period).
2	Weight	
3	Body surface	
4	Indications	Confirm cancer types for preventing an off-label regimen use.
5	Regimens	Confirm the main purpose of a regimen (Neoadjuvant therapy, adjuvant therapy, life-prolonging treatment, or palliative therapy).
6	Treatment date	Confirm treatment date.
7	Dosage	Confirm cumulative dose if the upper limit of the total dose is set for a drug.
8	Infusion rate	Special caution should be exercised for a drug with a different infusion rate between the initial treatment and 2nd and subsequent treatment courses.
9	Duration	Confirm whether an anticancer drug exceeds the upper limit of the dosing duration
10	Dose interval	Confirm the reason whether a rest period is shorter than the specified period.
11	Premedication	Confirm whether all premeditations described in package inserts are prescribed according to anticancer drugs.
12	Latest treatment history	Confirm whether a regimen is performed on a patient to prevent a regimen error (e.g., the use of a previous treatment regimen for initial treatment).
13	Laboratory test	Confirm examination date. (If there is an institution-specific rule, e.g., within the last several months, confirm whether the examination is performed within that period).
14	Urinalysis	

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 November 2023 doi:10.20944/preprints202311.0032.v1

15	Allergy history	Confirm whether a drug used in a regimen can be administered safely by checking a patient's allergy history.
16	Medical history	Confirm whether a drug used in a regimen can be administered safely by checking the side effects of the drug and a patient's medical history.
17	Concomitant drug	Confirm whether a drug used in a regimen can be administered safely by checking a patient's concomitant drugs (Drug interaction, duplicate medication, and contraindications for co-administration).
18	Oral anticancer drug	Confirm days on therapy, dosage, and dose interval in a regimen that concomitantly uses an oral anticancer drug.
19	History of B hepatitis virus	Confirm examination date (If there is an institution-specific rule, e.g., within the last several months, confirm whether the examination is performed within that period). Confirm whether HBV-DNA levels are measured within 1–3 months (periods vary depending on each anticancer drug) if a patient tested positive for HBs antibodies or HBc antibodies.

Confirming all 19 items is ideal; however, performing regimen checks entails work burdens. Furthermore, some institutions might have difficulty in performing some items owing to the absence of medical systems/resources. The aim of this prospective study was to examine the issues of these items to evaluate the possibility of their application to clinical practice.

2. Materials and Methods

2.1. Institutions analyzed

The National Hospital Organization is a Japanese hospital organization comprising 6 groups according to areas and managing 140 institutions. This prospective survey was performed on pharmacists of 14 hospitals, which consisted of 2, 5, 2, 2, 1, and 2 hospitals in the Hokkaido/Tohoku group, Kanto/Shinetsu group, Tokai/Hokuriku group, Kinki group, Chugoku/Shikoku group, and Kyusyu group, respectively to eliminate inter- and intragroup bias (Table 2). Among general hospitals willing to participate in this study, we included those with the number of claims for additional outpatient cancer chemotherapy of ≥ 500/year. Base hospitals for cancer treatment and hospitals with ≤2 departments to advocate within the following four categories were excluded: respiratory medicine, gastroenterology, surgery, and gynecology.

Table 2. Background of institutions.

Name	Beds	Electronic medical records	No. of pharmacists	No. of anticancer drug preparation
Hokkaido/Tohoku group A	500	Use	17	2544
Hokkaido/Tohoku group B	342	Use	12	6458
Kanto/Shinetsu Group A	560	Use	19	3603
Kanto/Shinetsu Group B	325	Non-use	11	1836
Kanto/Shinetsu Group C	250	Non-use	10	1890
Kanto/Shinetsu Group D	458	Use	13	4910
Kanto/Shinetsu Group E	350	Use	16	806
Tokai/Hokuriku group A	338	Use	16	3175
Tokai/Hokuriku group B	486	Use	26	3263
Kinki group A	304	Use	16	2099
Kinki group B	320	Use	15	3554
Chugoku/Shikoku group	424	Use	11	3707
Kyusyu group A	400	Use	16	4692
Kyusyu group B	300	Use	11	1481

 doi:10.20944/preprints202311.0032.v1

2.2. Regimens analyzed

The top 5 most frequent cancers in Japan (i.e., gastric, colorectal, lung, breast, and gynecological) were targeted. The most commonly used regimens reported in a preliminary questionnaire were analyzed. These included S-1+oxaliplatin (SOX) (gastric cancer), FOLFIRI+bevacizumab (Bev) (colorectal cancer), pembrolizumab/carboplatin+pemetrexed (CBDCA+PEM) (lung cancer), epirubicin+cyclophosphamide (EC) (breast cancer), and carboplatin+paclitaxel (TC) (gynecological cancer). Two regimens were allowed only for lung cancer because the rate of pharmacists who used these two drugs was the same in the preliminary questionnaire, and the number of immune checkpoint inhibitors used for the treatment has been increasing in Japan.

2.3. Investigation methods

2.3.1. Work time required for completing regimen checks

We investigated the duties of pharmacists when they performed regimen checks on inpatients and outpatients according to cancer types between July 1, 2019, and September 30, 2019. Between July 1 and August 12, pharmacists were asked to perform regimen checks using hospital-specific confirmation items (they were classified into the control group). Between August 13 and September 30, they were instructed to perform regimen checks using the recommended items (Table 1) (they were classified into the recommended item group). The same stopwatch was used to measure the time required for completing regimen checks in the two groups.

2.3.2. Number of confirmation items of regimen checks

Among the recommended items, those that pharmacists did not perform were tabulated.

2.3.3. Number and contents of doubt inquiries

We tabulated contents of doubt inquiries that arose from regimen checks performed by pharmacists.

2.3.4. Questionnaire

After performing the survey of the two groups, a questionnaire with a maximum score of 10 points (0–10 points) was administered to pharmacists who performed regimen checks. Pharmacists in the recommended item group were asked whether recommended items were potentially applied to clinical practice.

2.4. Statistical analysis

All statistical analyses were performed with EZR ver1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions, and is frequently used in biostatistics (Kanda 2013). A paired t-test was used for comparing questionnaire scores, and a P value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Time required for completing regimen checks

The number of confirmation items was 345 and 375 items in the control group and recommended item group, respectively. The mean time required for completing a regimen check (±standard deviation) was 4 minutes and 14 seconds (±1 minute and 50 seconds) and 6 minutes and 18 seconds (±1 minute and 7 seconds) in the control group and recommended item group, respectively. In B and C Hospitals (Kanto/Shinetsu group), where electronic medical records have not been introduced and

 doi:10.20944/preprints202311.0032.v1

data on prescription of anticancer drugs have been recorded on a paper, the mean time required for completing a regimen check was 4 minutes and 24 seconds (B Hospital) and 3 minutes and 10 seconds (C Hospital) in the control group as well as 9 minutes and 3 seconds (B Hospital) and 7 minutes and 24 seconds (C Hospital) in the recommended item group. The mean amount of time required for completing a regimen check was tabulated according to regimens, a previous history of cancer chemotherapy, cycles of chemotherapy, and certification of cancer-related associations. The results showed that a longer time was needed for all items in the recommended item group (Table 3).

Table 3. The mean time required for completing a regimen check according to regimens, previous cancer chemotherapy history, cancer chemotherapy cycles, and certification of cancer-related associations.

	Control group	Recommended item group
Total	4:14 SD (±1:50) (n=345)	6:18 SD (±1:7) (n=375)
Regimens		
SOX	5:15 (n=36)	6:18(n=62)
FOLFIRI+Bev	4:46 (n=79)	6:57(n=93)
Pembrolizumab	2:54(n=121)	5:25(n=93)
CBDCA+PEM	3:44 (n=23)	5:49(n=21)
EC	5:20 (n=19)	7:4 (n=19)
TC	5:23 (n=67)	6:28(n=87)
Previous history of cancer chemotherapy		
Initial	6:18 (n=44)	7:33(n=30)
2nd and onwards	3:56(n=301)	6:11(n=345)
Cycles of cancer chemotherapy regimens		
1st	6:1 (n=54)	8:20(n=41)
2nd and onwards	3:55(n=291)	6:3(n=334)
Certification of cancer-related associations		
Certified pharmacist	3:17 (n=58)	4:54 (n=55)
Non-certified pharmacist	4:26(n=287)	6:32(n=320)

SOX:S-1+oxaliplatin. FOLFIRI+Bev:FOLFIRI+bevacizumab. CBDCA+PEM: Carboplatin+pemetrexed. EC: Epirubicin+Cyclophosphamide. TC: carboplatin+paclitaxel. Time is expressed as mean.

3.2. Number of confirmation items of regimen checks

Among the recommended items, the mean number of items that pharmacists confirmed was 12.4 and 18.6 in the control and recommended items, respectively. Items that pharmacists did not confirm were urine protein (69 cases, 18.4%), an allergy history (4 cases, 1%), a previous history (2 cases, 0.5%), and a previous history of hepatitis B virus (69 cases, 18.4%).

3.3. Number and contents of doubt inquiries

The number of doubt inquiries was higher in the recommended item group than in the control group (41 vs. 27 cases). The number of doubt inquiries related to dosage, premedication, urinalysis, and a history of hepatitis B virus was higher in the recommended item group than in the control group (Table 4).

 doi:10.20944/preprints202311.0032.v1

Table 4. Doubt inquiry.

	Control group N=345	Recommended item group N=375
Number of doubt inquiries	27 cases (7.8%)	41cases (10.9%)
Body weight	1case (0.3%)	1case (0.3%)
Dosage	5cases (1.4%)	9 cases (2.4%)
Infusion rate	0cases (0%)	1 case (0.3%)
Dose interval	0cases (0%)	1 case (0.3%)
Premedication	4cases (1.2%)	7 cases (1.9%)
Blood biochemistry	5cases (1.4%)	0 cases (0%)
Urinalysis	1case (0.3%)	8 cases (2.1%)
Concomitant drugs	2 cases (0.6%)	1 case (0.3%)
Oral anticancer drug	1case (0.3%)	1 case (0.3%)
History of hepatitis B	8 cases (2.3%)	12 cases (3.2%)

3.4. Questionnaire

The respondents were the same 62 pharmacists classified into the control and recommended item groups (62 pharmacists for each group). The response rate was 100%. Regarding the question "Are current regimen checks conducted by pharmacists useful for performing safe cancer chemotherapy?"; the scores of the recommended item group showed a significant increase ($p<0.05$) (7.2 points in the control group vs. 8.2 points in the recommended item group). Regarding the question "Do you have confidence in current regimen checks performed by pharmacists?", the scores of the recommended item group significantly increased ($p<0.05$) (5.4 points in the control group vs. 6.2 points in the recommended item group). Only pharmacists in the recommended item group were asked to answer the question, "Did a recommended item affect the time required for completing a regimen check?" They responded that "More time was required because confirmation items increased" (44 pharmacists), "The number of confirmation items increased but time did not change" (15 pharmacists), "The number of confirmation items increased but time was shortened" (o pharmacists), and "Recommended items were not used because I did not understand them" (3 pharmacists). Regarding the question "Is distribution of recommended items into hospitals in Japan meaningful?" they responded that "It is meaningful for equalization of knowledge and methodology on cancer care" (34 pharmacists), "It is meaningful because there is no definition of regimen checks in my institution, although I may not utilize them" (8 pharmacists)," Further careful examination of confirmation items is required for obtaining a maximal benefit from them" (20 pharmacists), and "It is not meaningful because I am unable to use them" (0 pharmacists).

4. Discussions

In the present study, we created 19 items that should be confirmed in regimen checks and examined the possibility of their application to clinical practice. Pharmacists in the recommended item group confirmed almost all items, with a mean of 18.6 items. The mean time required for completing a regimen check was only 2 minutes and 4 seconds longer in the recommended item group than in the control group, suggesting that the potential application of the 19 recommended items to clinical practice in general hospitals other than cancer-designated hospitals was high.

Items that were not confirmed via numerous pharmacists were urinalysis and history of B hepatitis virus. Given that the risk of proteinuria may increase after the use of molecular targeting drugs such as bevacizumab, confirmation of urine protein levels is essential. Furthermore, confirmation of urinalysis was highly recommended because type 1 diabetes secondary to immunotherapy is reported. The confirmation of a history of B hepatitis virus was important because anticancer drugs, primarily rituximab, caused reactivation of this disease, which had serious consequences (Tsutsumi et al. 2015). The following theorizes the reason for such unsuccessful confirmation. Examination orders are required to confirm urinalysis and history of B hepatitis virus; however, in general, in hospitals that participated in the study, many treatments are provided by

 doi:10.20944/preprints202311.0032.v1

physicians without special certification in cancer chemotherapy (Fukuoka 2009). Thus, they were less likely to recognize the importance of examining the two items. The 19 recommended items were created based on items used in cancer-designated hospitals. This solid evidence may assist pharmacists in explaining their decision to physicians after they identify an error in physician's prescription orders in regimen checks using the 19 recommended items.

In terms of work burden, the mean time required for completing a regimen check was 2 minutes and 4 seconds longer in the recommended item group than in the control group. More than 70% of the pharmacists responded that more time was required to complete a regimen check because of increased confirmation items. Such a response raises concerns regarding the potential application of the 19 recommended items to institutions with insufficient pharmacists. As a measure against such a burden on pharmacists, detailed data on items confirmed by pharmacists should be recorded after they perform regimen checks in patients who receive initial cancer chemotherapy. The difference in time required for completing a regimen check was compared between patients who received initial treatment and those who underwent second and subsequent treatments. The results showed that it was 1 minute and 22 seconds in the recommended item group and 2 minutes and 22 seconds in the control group. This one-minute difference between the two groups suggested that pharmacists needed to confirm many items, even in patients in the control group, if they were cancer chemotherapy-naïve patients.

Among the recommended items, data related to certain items, including an allergy history, were duplicated if pharmacists recorded them after initial regimen checks. This may reduce the time required for completing a regimen check in the second and subsequent treatments. In addition to regimen checks, hospital pharmacists in Japan are responsible for several duties, such as preparing anticancer drugs and dosing instructions. With this background, performing regimen checks is challenging for the same pharmacist each time. The time required for completing a regimen check was expected to be shortened if pharmacists who perform regimen checks document detailed data on cancer chemotherapy- naïve patients in the patient's chart or paper.

Intergroup comparisons were performed to measure the difference in time required for completing a regimen check in two institutions where electronic medical records were not introduced. The results showed that the required time was 4 minutes and 39 seconds and 4 minutes and 14 seconds. These results were two minutes longer than the mean time of all institutions. This difference in time may be attributable to a problem related to systems. Information on recommended items should be obtained from the patient's chart, thereby inevitably requiring more time in institutions where electronic medical records have not been introduced. The percentage of hospitals that introduced electronic medical records has been increasing every year. However, according to a survey of medical institutions in Japan conducted by the Ministry of Health, Labour and Welfare in 2020, this percentage was 57.2%, suggesting that many hospitals continued to use paper-based records (Medical facility survey, Tokyo 2020). In institutions without electronic medical records, the efficacy of regimen checks may be improved if pharmacists who perform regimen checks cooperate with hospital pharmacists who check patients' charts every day and ward nurses, although only the physician's contact information was given in this study.

The number of doubt inquiries was higher in the recommended item group than in the control group (41 cases vs. 27 cases). An increase in confirmation items may be associated with safe cancer chemotherapy. The results of our questionnaire supported this hypothesis. Specifically, the scores of questions related to the usefulness of and confidence in current regimen checks were higher in the recommended item group than in the control group. Furthermore, the percentage of pharmacists who positively responded to the question (i.e., those who answered that recommended items are meaningful to equalize and define knowledge and methodology on cancer chemotherapy) was 68%, indicating that the recommended items will be distributed to many institutions in Japan.

This study consisted of two stages, with each stage lasting for approximately 1.5 months. Thus, the learning curve of the pharmacists who performed regimen checks was not taken into consideration, which was a limitation of this study. If regimen checks using the recommended items are continued for 6 months or 1 year, the accuracy of doubt inquiries was expected to increase. The

 doi:10.20944/preprints202311.0032.v1

results of our study with a duration of 1.5 months may be insufficient. However, this study aimed to evaluate whether the recommended items were applied to clinical practice. The results of this study suggest the possibility of their application, which is significant.

We instructed the pharmacists to confirm only the recommended items when they performed regimen checks. We did not give sufficient attention to their knowledge of each anticancer drug and regimen. This indicates that pharmacists with insufficient expertise may not effectively use the recommended items. According to a report by Brian et al. (2017), an association of pharmacists' knowledge with successful implementation of regimen checks becomes strong in a complex regimen (i.e., several drugs are combined). Development of methods according to the complexity of regimens is required. Our questionnaire showed that 32% of the pharmacists responded that the contents of regimen checks should be scrutinized before the concept of regimen checks was standardized in Japan. A study by Ohta et al. has shown that the most common source of information used for regimen checks is package inserts (Ohta et al. 2021). However, finding information on regimen check items used as criteria for administration and required for expertise, such as supportive medications and laboratory values is challenging only in package inserts. Information sources other than package inserts in Japan include interview forms released by pharmaceutical companies, a guide for appropriate use of medication, the risk management plan, and specialized books released from cancer treatment collaborative base hospitals (Satou et al. 2016). When the recommended items are introduced into each institution, using these useful materials and package inserts is recommended to establish a detailed check tool according to regimens.

Although six groups from the National Hospital Organization were incorporated in the present study, the results were composed of only 14 facilities. Therefore, it was our understanding that we could not completely prevent bias because the number of anticancer agents and the number of pharmacists varied in each facility; this was true even in general hospitals other than cancer treatment base hospitals and other hospitals. In addition, although the survey targeted regimens with high usage rates among the five cancers with the highest incidence rates in Japan, taking the recent increase in the combination of immune check inhibitors and cytotoxic anticancer drugs into consideration. Furthermore, we did not account for the patients' background, so it is possible that regimen checks were performed at some facilities on patients with a high history or concomitant medications. Considering the limitations of these research backgrounds, increasing the number of facilities and studying the latest treatment details is necessary. To accumulate the evidence of the 19 recommended items and create Japanese guidelines for regimen checks, we will distribute these items as a manual to hospitals of the National Hospital Organization that perform cancer chemotherapy.

Table 5. Results of questionnaire.

	Control group N=62	Recommended item group N=62	*P* value
Are current regimen checks performed by pharmacists useful to ensure safe cancer chemotherapy?	7.2 points	8.2 points	<0.05
Do you have confidence in current regimen checks performed by pharmacists?	5.4 points	6.2 points	<0.05
Did the 19 recommended items affect the time required for completing a regimen check? (Select one that applies)			
(1) More time was required because number of confirmation items increased		44 pharmacists	
(2) The number of items confirmation items increased; however, the time did not change		15 pharmacists	
(3) The number of confirmation items increased; however, the time was shortened		0 pharmacists	
(4) I was unable to use 19 recommended items because I did not understand them		3 pharmacists	

 doi:10.20944/preprints202311.0032.v1

Is the distribution of 19 recommended items to hospitals in Japan meaningful? (Select one that applies)		
(1) It is meaningful for the equalization of knowledge and methodology in cancer care	34 pharmacists	
(2) It is meaningful owing to the absence of a definition of regimen checks in my institution, although I may not utilize them	8 pharmacists	
(3) Further careful examination of confirmation items is required to obtain a maximal benefit from them	20 pharmacists	
(4) It is not meaningful because I am unable to use them	0 pharmacists	

Supplementary Materials: There is no supplementary materials.

Author Contributions: Conceptualization, D.U., S.S. and T.O.; methodology, A.S., Y.O., D.K., Y.R., R.U., H.M., M.I., A.T., Y.K., M.K., and M.U.; validation, K.I., T.K. and M.Y.; formal analysis, D.U. and T.O.X.; investigation, D.U. and T.O.; writing—original draft preparation, D.U.; writing—review and editing, T.O. and S.S.; supervision, K.I., T.K. and M.Y.; project administration, D.U.; funding acquisition, D.U. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by a 2018 National Hospital Organization Pharmacist Association research grant.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Tokyo Hospital (approval No. 440-190002).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to confidential issues.

Acknowledgments: We thank the head of the pharmacy department and pharmacists of each group of the National Hospital Organization for their cooperation in this study. We thank Crimson Interactive Pvt. Ltd. (Ulatus) – www.ulatus.jp for their assistance in manuscript translation and editing.

Conflicts of Interest: The authors declare no conflict of interest.

References

Díaz-Carrasco MS, Pareja A, Yachachi A, Cortés F, Espuny A (2007) Prescription errors in chemotherapy. Farm Hosp 31: 161–164. doi: 10.1016/s1130-6343(07)75364-3.

Freeman PR, Curran GM, Drummond KL, Martin BC, Teeter BS, Bradley K, Schoenberg N, Edlund MJ (2019) Utilization of prescription drug monitoring programs for prescribing and dispensing decisions: results from a multi-site qualitative study. Res Social Adm Pharm 15: 754–760. doi: 10.1016/j.sapharm.2018.09.007.

Fukuoka M (2009) Oncology in cancer care. The Japanese Society of Internal Medicine 98: 1–4.

Griffin MC, Gilbert RE, Broadfield LH, Easty AE, Trbovich PL, Griffin MC, Gilbert RE, Broadfield LH, Easty AE, Trbovich 4.PL (2016) ReCAP: Comparison of Independent Error Checks for Oral Versus Intravenous Chemotherapy. J Oncol Pract 12: 168–169; e180. doi: 10.1200/JOP.2015.005892.

Hayashi M, Yamatani A, Funaki H, Miyamoto K (2015) Pharmacoeconomic effect of compliance with pharmacist's intervention based on cancer chemotherapy regimens: a cohort study. J Pharm Health Care Sci 1: 10. doi: 10.1186/s40780-014-0007-y.

Medical facility survey. Tokyo: Ministry of Health, Labor and Welfare (2020). Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryou/johoka/index.html (access date: **2022**, **9**/**19**).

Jacobson JO, Polovich M, Gilmore TR, Schulmeister L, Esper P, LeFebvre KB, Neuss MN (2012) Revisions to the 2009 American Society of Clinical Oncology/oncology nursing Society chemotherapy administration safety standards: Expanding the scope to include inpatient settings. J Oncol Pract 8: 2–6. doi: 10.1200/JOP.2011.000339.

Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48: 452–458. doi: 10.1038/bmt.2012.244.

Kohler DR, Montello MJ, Green L, Huntley C, High JL, Fallavollita A, Goldspiel BR (1998) Standardizing the expression and nomenclature of cancer treatment regimens. American Society of Health System Pharmacists (ASHP), American Medical Association (AMA), American Nurses Association (ANA). Am J Health Sys Pharma 55: 137–144.

Mitchell G, Porter S, Manias E (2021) Enabling sustained communication with patients for safe and effective management of oral chemotherapy: A longitudinal ethnography. J Adv Nurs. 77: 899–909. doi: 10.1111/jan.14634.

Mulac A, Taxis K, Hagesaether E, Gerd Granas A (2021) Severe and fatal medication errors in hospitals: findings from the Norwegian incident reporting system. Eur J Hosp Pharm 28: e56–e61. doi: 10.1136/ejhpharm-2020-002298.

Ohta T, Suzuki S, Shinohara A, Ohashi Y, Ueki D, Konuma D, Ryushima Y, Udagawa R, Kawasaki T, Yamaguchi M (2021) Needs of chemotherapy regimen checks produce: from the survey on chemotherapy regimen checks performed by pharmacists in hospitals other than designated cancer hospitals in Japan. Eur J Oncol Pharm 4: 4.

Ranchon F, You B, Salles G, Vantard N, Schwiertz V, Gourc C, Gauthier N, Guédat MG, Souquet PJ, Freyer G, Trillet-Lenoir V, Rioufol C (2013) Improving cancer patient care with combined medication error reviews and morbidity and mortality conferences. Chemotherapy 59: 330–337. doi: 10.1159/000358190.

Raymond G, Kerry P (2012) Chemotherapy medication errors in a pediatric cancer treatment center: prospective characterization of error types and frequency and development of a quality improvement initiative to lower the error rate. Pediatr Blood Cancer 60: 1320–1324.

Sato H, Ohira H, Murakami T, Kanetaka Y, Murakami T, Izumi H, Hashimoto Y, Komori H (2016) Comparison between risk listed in the risk management plan and the product labeling of the drug package insert. Jpn J Drug Inform 17: 205–208.

Suzuki S, Sakurai H, Kawasumi K, Tahara M, Saito S, Endo K (2016) The impact of pharmacist certification on the quality of chemotherapy in Japan. Int J Clin Pharm 38: 1326–1335. doi: 10.1007/s11096-016-0374-6.

Suzuki S, Chan A, Nomura H, Johnson PE, Endo K, Saito S (2017) Chemotherapy regimen checks performed by pharmacists contribute to safe administration of chemotherapy. J Oncol Pharm Pract 23: 18–25. doi: 10.1177/1078155215614998.

Tsutsumi Y, Yamamoto Y, Ito S, Ohigashi H, Shiratori S, Naruse H, Teshima T (2015) Hepatitis B virus reactivation with a rituximab-containing regimen. World J Hepatol 7: 2344–2351. doi: 10.4254/wjh.v7.i21.2344.

von Grünigen S, Geissbühler A, Bonnabry P (2022) The safe handling of chemotherapy drugs in low- and middle-income countries: an overview of practices. J Oncol Pharm Pract. 28: 410-420. doi: 10.1177/1078155221995539.

Weiss BD, Scott M, Demmel K, Kotagal UR, Perentesis JP, Walsh KE (2017) Significant and sustained reduction in chemotherapy errors through improvement science. J Oncol Pract 13: e329–e336. doi: 10.1200/JOP.2017.020842.