Salient Features and Outline of the Joint Japanese Guidelines for Safe Handling of Cancer Chemotherapy Drugs

Kiyoko Kanda¹, Kazue Hirai², Keiko Iino³, Hisanaga Nomura⁴, Hisateru Yasui⁵, Taro Kano⁶, Chisato Ichikawa⁷, Sumiko Hiura⁸, Tomoko Morita⁹, Ayako Mitsuma⁹, Hiroko Komatsu¹⁰

¹Department of Nursing, Graduate School of Health Sciences, Gunma University, Gunma, ²School of Nursing, Faculty of Medicine, Tokyo Medical University, Tokyo, ³Department of Nursing, National College of Nursing, Tokyo, ⁴Department of Pharmacy, National Cancer Center Hospital East, Chiba, ⁵Department of Medical Oncology, Kobe City Medical Center General Hospital, Hyogo, ⁶Department of Nursing, Gunma Prefectural College of Health Sciences, Gunma, ⁷Department of Nursing, National Cancer Center Hospital East, Chiba, ⁸Department of Pharmacy, Toho University Ohashi Medical Center, Tokyo, ⁹Department of Clinical Oncology and Chemotherapy, Nagoya University Graduate School of Medicine, Nagoya, ¹⁰Department of Nursing, Faculty of Nursing and Medical Care, Keio University, Tokyo, Japan

Corresponding author: Kiyoko Kanda, PhD, RN, PHN
Professor, Department of Nursing, Graduate School of Health Sciences, Gunma University, Gunma, Japan
Tel: +81272208929; Fax: +81272208929
E-mail: kkanda@gunma-u.ac.jp
Received: February 02, 2017, Accepted: April 25, 2017

ABSTRACT

The purpose of this paper is to introduce the outline and describe the salient features of the “Joint Guidelines for Safe Handling of Cancer Chemotherapy Drugs” (hereinafter, “Guideline”), which were published in July 2015. The purpose of this Guideline is to provide guidance to protect against occupational exposure to hazardous drugs (HDs) to all medical personnel involved in cancer chemotherapy, including physicians, pharmacists, and nurses and home health-care providers. The Guideline was developed according to the Medical Information Network Distribution Service guidance for developing clinical practice guidelines, with reference to five authoritative guidelines used worldwide. PubMed, Cumulative Index to Nursing and Allied Health Literature, Ichushi-Web, and Cochrane Central Register of Controlled Trials were used for a systematic search of the literature. Eight clinical questions (CQs) were eventually established, and the strength of recommendation for each CQ is presented based on 867 references. The salient features of the Guideline are that it was jointly developed by three societies (Japanese Society of Cancer Nursing, Japanese Society of Medical Oncology, and Japanese Society of Pharmaceutical Oncology), contains descriptions including the definition of HDs and the concept of hierarchy of controls, and addresses exposure control measures during handling of chemotherapy drugs. Our future task is to collect additional evidence for the recommended exposure control measures and to assess whether publication of the Guideline has led to adherence of measures to prevent occupational exposure.

Key words: Hazardous drugs, medical stuff, safe handling of cancer chemotherapy

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Cite this article as: Kanda K, Hirai K, Iino K, Nomura H, Yasui H, Kano T, et al. Salient features and outline of the joint Japanese guidelines for safe handling of cancer chemotherapy drugs. Asia Pac J Oncol Nurs 2017;4:304-12.
Introduction

In July 2015, the first Japanese Guidelines for exposure control measures, namely, the “Joint Guidelines for Safe Handling of Cancer Chemotherapy Drugs,” were published jointly by three societies, namely, Japanese Society of Cancer Nursing (JSCN), Japanese Society of Medical Oncology (JSMO), and Japanese Society of Pharmaceutical Oncology (JASPO). Anticancer drugs, which are hazardous drugs (HDs), exert cytotoxic effects on cancer cells, but many have also been shown to have mutagenicity, teratogenicity, and carcinogenicity. However, in Japan, the concept of HD has not yet become widely recognized, and individual medical institutions have implemented their own exposure control measures by referring to European and US Guidelines without clear specification of criteria for the exposure control measures. Thus, there are differences in the exposure control measures adopted among hospitals and clinic, and small- and medium-sized hospitals, in fact, do not have sufficient exposure control measures in place. Medical personnel, including physicians, nurses, and pharmacists, have minimal education about control measures of HDs or exposure to control measures during their basic years of education and learn them only during postgraduate education, clinical experience, and on the job training.

In addition, Guidelines that have so far been published in Japan have mainly focused on the exposure control measures that must be adopted during preparation of the drugs. However, exposure to HDs is not limited to the drug preparation process, and comprehensive control measures, including during administration of the drugs and environmental protection, are important and need to be adopted by health-care practitioners, including physicians, nurses, and pharmacists, in cooperation with the local government. The present guidelines were developed to promote occupational exposure control measures, including those to be adopted other handling activities including administration of the drugs and handling of excreta (for which nurses are predominantly in charge), for all occupations involved in the handling of HDs. The salient features and outline of the Joint Guidelines for Safe Handling of Cancer Chemotherapy Drugs (hereinafter, the Guidelines) are introduced below.

Four Salient Features of the Guidelines

Salient feature 1

The Guidelines were published jointly by three societies (JSCN, JSMO, and JASPO) consisting of professionals handling anticancer drugs and are therefore expected to promote adoption of control measures by all health-care practitioners who handle HDs, including physicians, pharmacists, and nurses. JSCN was founded in 1987 and has a membership of approximately 6000. JSMO was established in 1987 and has a membership of 9000. JASPO was established in 2012 and has a membership of approximately 2200.

Salient feature 2

Clarification of the definition of HDs and description of the concept of HDs: The term HDs is not yet sufficiently well recognized in Japan, and the Japanese Society of Hospital Pharmacists introduced the concept of HDs in “Research and Investigation for the Development of Guidelines for Safe Handling of Anticancer Drugs.”[1] In this Guideline, a HD is defined as one that exhibits one or more of the following six characteristics: (1) carcinogenicity, (2) teratogenicity or other developmental toxicity, (3) reproductive toxicity, (4) organ toxicity at low doses, (5) genotoxicity in humans or animals, and (6) newer drugs with a chemical structure and toxicity profile similar to those of an existing drug determined hazardous by the above criteria.[2]

Salient feature 3

Introduction of the concept of hierarchy of controls [Figure 1]: The concept of “hierarchy of controls” is used to eliminate or minimize the risk based on risk management in occupational safety management. The US Oncology Nursing Society (ONS) emphasizes “protection, such as prevention of diffusion and prevention of exposure” (protection) during drug administration, handling of excreta, etc. The International Society of Oncology Pharmacy Practitioners described that “containment of exposure sources by protection” (prevention) is important during drug preparation.[3] Exposure control measures described in the Guidelines are not limited to those that only need to be adopted during the drug

---

Figure 1: Hierarchy of controls
preparation and are thus in accordance with the idea of the ONS. Explicitly, as shown in Figure 1, the exposure control measures consist of (1) elimination/substitution, this is not feasible for chemotherapy drugs, (2) engineering controls, (3) administrative controls, (4) work practice controls, and (5) personal protective equipment (PPE). Because measure (1) is the most effective and measure (5) is the least effective, it is desirable to implement the measures in sequential order beginning with measure (1).

**Salient feature 4**

Coverage of all the steps at which exposure control measures must be implemented, not limited to measures to be adopted during the drug preparation in Japan: There is a wide range of exposure opportunities, such as during preparation, administration, disposal, drug transportation, and handling of body fluids. Exposure control measures are required for all professionals engaged in various HD handling procedures, not limited to those involved in the preparation. Coverage of the handling procedures is one of the salient features of the guidelines.

**Outline of the Guidelines**

**Purpose and health-care workers covered**

The purpose of the guidelines is to provide best practices for preventing occupational exposure to HDs to all health-care workers who handle chemotherapy drugs, including physicians, pharmacists, nurses, shipping and receiving personnel, custodial workers, laundry workers, and waste handlers. The Guideline applies to hospitals, ambulatory health-care settings, and home healthcare.

**Development procedure**

A Joint Committee of the three societies was organized to develop the Guideline by referring the 2007 and 2014 “Medical Information Network Distribution Service Guidance for Developing Clinical Practice Guidelines.” Information in five authoritative safe handling guidelines [Table 1][5] was examined to systematize the background knowledge. The flow of development of the Guideline is shown in Figure 2.

**Systematic literature search and screening**

A literature search on Safe Handling of Cancer Chemotherapy Drugs was conducted of the following databases: PubMed, Cumulative Index to Nursing and Allied Health Literature, and Ichushi-Web. The Cochrane Central Register of Controlled Trials of the Cochrane Library was also searched for any intervention studies. The search period was not limited because little evidence has been published in this field.

**Evidence level and strength of recommendation**

The evidence level and strength of recommendation in the Guidelines were determined according to the criteria established by the committee [Tables 2-4][5].

**Validity test**

Draft clinical questions (CQs) proposed by each of the societies were discussed by the Committee. A draft explanation of the CQs and strengths of recommendation were prepared based on the results of the literature search. The draft was reviewed using the Delphi method. Furthermore, the draft was assessed by the members of the assessment committee of the three societies based on the Appraisal of Guidelines Research and Evaluation II, and public comments were collected and reviewed by each of the three societies to complete the final version of the Guidelines.

**Results**

**Strength of recommendation and summary of clinical questions**

The databases were searched for 22 CQs, but no articles were identified for some of the CQs, and consequently, 8 CQs were selected [Table 5]. Of these, CQ1, 3, and 7[6] are introduced below.

**Clinical question 1:** Is consideration of the influence of occupational exposure to hazardous drugs on fertility recommended?

Many studies have reported that HDs have an adverse impact on pregnancy in patients receiving treatment with...
HDs. Studies on the influence of occupational exposure to HDs on pregnancy have been conducted since the 1980s and have reported an increase in the incidence of miscarriages (Selevanet et al.,[7] 1985, Stücker et al.,[8] 1990), exposure-duration-dependent congenital anomalies (Hemminki et al.,[9] 1985), low-birth weight and congenital anomalies (Peelen et al.,[10] 1999), infertility (Valanis et al.,[11] 1999), etc.[12]

Results of case–control studies and questionnaire surveys have demonstrated a significant relationship between exposure to HDs and outcomes on pregnancy, but it should be noted that recall bias tends to occur when an exposure history is obtained.

Dranitsaris et al. conducted a meta-analysis of seven studies on the relationship of exposure to anticancer drugs to spontaneous abortion, congenital anomalies and stillbirth, including the above studies. The meta-analysis concluded that exposure to anticancer drugs was not significantly related to the occurrence of congenital anomalies (four cases) or stillbirth (two cases) (odds ratio [OR] =1.64, 95% confidence interval [CI]: 0.91–2.94 for congenital anomalies; OR = 1.16, 95% CI: 0.73–1.82 for stillbirth) but was related to the occurrence of spontaneous abortion (five cases) (OR = 1.46, 95% CI: 1.11–1.92), indicating that female workers handling anticancer drugs are at a slightly elevated risk of spontaneous abortions (evidence level A).[13] With two exceptions, all the studies used in this meta-analysis were published in or after 1990, and dissemination of exposure control measures based on the guidelines may have made the influence less obvious.

A case–control study conducted by Skov et al. in Denmark concluded that the influence of occupational exposure to HDs on the risk of fetal malformations, miscarriage, low-birth weight, and premature delivery is reduced by implementation of appropriate safe handling and preventive measures.[14,15]

Fransman et al. evaluated the influence on health by conducting a comparison between exposed and nonexposed (control) nurses in a total of 4393 nurses in the
Clinical question 3: Is the use of a closed-system drug transfer device recommended during the preparation of hazardous drugs?

Even when exposure controls such as PPE or a safety are used, there is still a risk of exposure to HDs. A closed-system drug transfer device (CSTD) has been reported to be useful for avoiding this risk.[20–25]

Sessink et al. reported that the use of CSTD significantly reduced the level of surface contamination by cyclophosphamide hydrate on the safety cabinet surface, front part of the safety cabinet, floor, and counter as compared to that observed with the conventional standard preparation technique using needles and syringes, indicating that the use of CSTD can protect health-care workers against exposure to HDs (evidence level C).[20] Furthermore, the study also reported that the use of CSTD reduced surface contamination not only by cyclophosphamide hydrate but also by ifosfamide and fluorouracil as compared to that observed with the conventional standard preparation technique (evidence level C).[21]
Favier et al. reported that comparison of the levels of environmental contamination in the preparation of doxorubicin hydrochloride and cyclophosphamide hydrate before and after the introduction of CSTD revealed that the frequency of contamination of the work table decreased from 88% to 6% after the introduction of CSTD, the frequency of surface contamination by HDs decreased from 84% to 0%, and the frequency of environmental contamination decreased from 18% to 6% (evidence level C). [23]

Yoshida et al. reported that the use of CSTD reduced contamination by cyclophosphamide hydrate, measured by surface swabbing, of gloves, work surface inside the safety cabinet, front surface of the air inlet of the safety cabinet, stainless trays in the preparation room, work tables, and floor. In addition, the amount of cyclophosphamide hydrate decreased in 24-h urine samples of pharmacists who were involved in the drug preparation (evidence level C). [24]

Wick et al. reported that the use of CSTD in a class II safety cabinet reduced the levels of urine contamination by cyclophosphamide hydrate and ifosfamide (evidence level C). [25]

De Ausen et al. reported that examination of the leakage of 99mTc solution using three CSTDs (ChemoClave®, OnGuard® and PhaSeal®) revealed that the leakage was smaller when PhaSeal® was used than when ChemoClave® or OnGuard® was used (evidence level C). [26] Nishigaki et al. reported that comparison of the levels of contamination by cyclophosphamide hydrate during preparation using Clave® Oncology System (ChemoClave®) and PhaSeal® showed that the level of contamination was lower when ChemoClave® (1.1 ng [0.2–254.0 ng]) or PhaSeal® (0.5 ng [0.1–2.0 ng]) was used than during conventional preparation using needles and syringes (2.5 ng [0.4–100.1 ng]) (evidence level C). [27] Sato et al. reported based on measurement of the amount of environmental contamination by cyclophosphamide hydrate before and after the introduction of Chemosafe® that the amount of contamination on the front surface inside the safety cabinet, the floor under the safety cabinet, and the work table decreased after the introduction of Chemosafe® (evidence level C). [28]

Hama et al. reported that the use of CSTD reduced contamination, including during the preparation of nonvolatile drugs and preparation of drug infusion pumps (evidence level C). [29]

From the above, drug preparation using CSTD is associated with reduced contamination levels and concentrations of HDs and the exposure levels of workers involved in the preparation of HDs compared to conventional drug preparation using needles and syringes. Furthermore, a decrease in the surface contamination by prepared drugs and in contamination of safety cabinets leads to a decrease in the level of environmental contamination. Many of the studies that provided results in support of the use of CSTD were conducted with small study samples and the evidence levels are low, but it is necessary to use CSTD taking into consideration the structure and characteristics of the device for preventing occupational exposure.

Clinical question 7: Is the use of personal protective equipment recommended in hazardous drug administration?

There have been reports on the usefulness of PPE during preparation and administration of HDs, but there have been no reports on the usefulness of PPE exclusively in administration.

In regard to the exposure opportunities during HD administration, Terui et al. [20] examined the leakage of drug solutions during the process of preparation and administration. They reported dispersion into the surroundings during the drug preparation, contamination of needles used during the preparation, contamination of the surroundings by HD priming, and leakage in cases where tube flushing with saline failed to be performed when infusion bags were exchanged or when the infusion tubes were removed after completion of HD administration (evidence level C).

Villarini et al. [30] investigated gene mutations according to the presence or absence of environmental contamination and use of PPE (gloves and masks) during the preparation and administration in an anticancer drug exposure group consisting of 52 subjects (workers involved in the preparation, transportation, administration or disposal of fluorouracil or cytarabine) and a control group consisting of 52 subjects (workers not exposed to anticancer drugs). They found that the frequency of genetic damage was significantly higher in the exposure group (P < 0.0001), but that in the exposure group, the frequency of primary DNA damage was significantly lower in the subjects who wore PPE (P = 0.045), indicating the usefulness of PPE (evidence level C).

In addition, Undeger et al. [31] reported that the frequency of genetic damage was significantly higher in an anticancer drug exposure group consisting of 30 nurses (who were involved in the preparation and administration of cyclophosphamide hydrate, methotrexate, fluorouracil, doxorubicin hydrochloride, bleomycin hydrochloride, cisplatin, vinblastine sulfate, vincristine sulfate, ifosfamide, or etoposide) than in a control group consisting of 30 nurses (who had not been exposed to any anticancer drugs) (P < 0.001). Furthermore, the study reported that the frequency of genetic damage was significantly higher in
nurses who did not wear PPE ($P < 0.001$), indicating the usefulness of PPE (evidence level C).

Thus, it was confirmed that contamination tends to occur in some operations and situations when HDs are administered intravenously, indicating that the use of appropriate procedures and PPE is important to prevent exposure of health-care workers involved in administration of HDs.

**Personal protective equipment**

The Committee originally created a list of PPE recommended at each step of handling of HDs considering the present state in Japan, based on the PPE guidance provided in the 2014 NIOSH HD list [Table 6].[32]

**Summary and Future Tasks**

Interest in occupational exposure and exposure control measures has increased rapidly in Japan, since the publication of the Guidelines. However, at present, there are differences in the level of understanding and in the adoption of control measures among different occupations within an organization. For example, during drug preparation, safety cabinets and PPE have been commonly used. There is a universal health insurance system in Japan, wherein part of the medical expenses is paid by the Japanese government. Since 2012, 1,000 yen (8.9 US$) has been added to the medical reimbursement when CSTD is used during preparation of the three highly volatile antineoplastic agents, ifosfamide, cyclophosphamide hydrate, and bendamustine hydrochloride. Since 2016, 1,800 yen (16 US$) has been added to the medical reimbursement for all anticancer drugs. By comparison, during the step of administration, nurses generally use common infusion sets for administration, and currently, they insert bottle needles into infusion bags containing anticancer drugs and prime infusion bags with anticancer drugs at the bedside. Future tasks are to obtain cooperation from health-care practitioners and to promote the use of CSTD during administration of HDs.

To achieve these tasks, entrepreneurs and administrators using the Guideline are expected to develop an interest in occupational exposure control measures and take the lead

---

**Table 6: Personal protective equipment recommended in each step**

| Dosage form                  | Operation                                      | Gloves$^{a}$ (©: Double, O: Single) | Gown | Safety glasses | Mask$^{b}$ (©: N95, O: Surgical mask) |
|-----------------------------|------------------------------------------------|-----------------------------------|------|----------------|----------------------------------------|
| PPE required for handling HD| Injection                                      | ©                                 | O    | O              | ©$^{b}$                                 |
|                             | Preparation                                    | ©                                 | O    | O              | ©$^{b}$                                 |
|                             | Administration$^{a}$                           | ©                                 | O    | O              | ©$^{b}$                                 |
| Oral drugs                  | Tablet/ capsule                                | O$^{j}$                           | ×    | ×              | ×                                      |
|                             | Internal use assistance                        | O                                 | O    | O              | ©                                      |
|                             | Simple suspension                              | ©                                 | O    | O              | O                                      |
|                             | Tube administration                            | ©                                 | O    | O              | O                                      |
|                             | Powder                                         | ©                                 | O    | O              | ©$^{b}$                                 |
|                             | Dispensing                                     | ©                                 | O    | O              | ©$^{b}$                                 |
|                             | Internal use assistance                        | ©                                 | O    | O              | ©$^{b}$                                 |
|                             | Inhalant                                       | ©                                 | O    | O              | ©                                      |
|                             | Preparation                                    | ©                                 | O    | O              | ©                                      |
|                             | Inhalation assistance                          | ©                                 | O    | O              | ©                                      |
|                             | Ointment                                       | ©                                 | O    | ×              | ×                                      |
|                             | Suppository                                    | ©                                 | O    | ×              | ×                                      |
|                             | All dosage forms                               | ©                                 | ×    | ×              | O                                      |
| PPE required during care of patients receiving HD | Activity                                       | Gloves$^{a}$ (©: Double, O: Single) | Gown | Safety glasses | Mask$^{b}$ (©: N95, O: Surgical mask) |
|                             | Handling of excreta or vomit                   | O                                 | O$^{j}$ | O$^{j}$ | O                                      |
|                             | Handling of linens contaminated with excreta or vomit | O | O$^{j}$ | O$^{j}$ | O                                      |
|                             | Handling of linens                             | ©                                 | O    | O              | ©                                      |
| PPE required for cleaning of the HD administration environment, etc. | Activity                                       | Gloves$^{a}$ (©: Double, O: Single) | Gown | Safety glasses | Mask$^{b}$ (©: N95, O: Surgical mask) |
|                             | Cleaning of spillsh                            | O                                 | ×    | ×              | O                                      |
|                             | Routine indoor cleaning                        | O                                 | ×    | ×              | O                                      |
|                             | Transportation of HD waste                     | O                                 | ×    | ×              | O                                      |

$^{a}$ is double gloved and $^{b}$ is single gloved when doing each practice. $^{c}$ is N95 and $^{d}$ is Surgical mask used when doing each practice. "A surgical mask may be acceptable when a safety cabinet, isolator, or CSTD is used on the assumption that appropriate preparation procedures are used," "Intravenous, subcutaneous, intramuscular, or intraluminal injection," "A surgical mask may be acceptable when CSTD is used on the assumption that appropriate administration procedures are used," "Single gloves should be used or direct contact with the hands should be avoided when handling the drug," "When the use of a surgical mask is inevitable, the face should be kept away from the drug when handling it to avoid absorbing it by inhalation," "Gowns that prevent the penetration of liquid substances can be used," "A face shield should be selected, particularly when the drug may disperse," "Shoe covers should be additionally used according to the state of contamination. O: Necessary, ×: Usually unnecessary, HD: Hazardous drugs, PPE: Personal protective equipment, CSTD: Closed-system drug transfer device. Cited and modified from: JSCN/JSMO/JASPO Joint Guidelines for Safe Handling of Cancer Chemotherapy Drugs, Kanehara Co., Ltd, p 45.
in promoting best practices. Furthermore, it is necessary to establish multidisciplinary teams to systematically implement exposure control measures to protect health-care workers who handle HDs.

In addition, while the databases were first searched using 22 CQs to develop the Guidelines, only 8 CQs were ultimately used because there was no published evidence for the remaining CQs. The Guidelines focus on occupational exposure control measures and do not specifically describe the details of the methods and instructions for patients and their families. Outpatients receiving chemotherapy and patients taking oral anticancer drugs are increasing in number, and establishment of evidence allowing patients and their families to follow the safest practices for their environment is required. Exposure to HDs is a field in which intervention studies involving human subjects cannot be conducted and it is difficult to conduct studies with high-evidence levels, but it is necessary to continue studies in the future.

The Guidelines were developed in cooperation with nurses, physicians, and pharmacists by making good use of their expertise. Therefore, problems in each occupation were adopted as CQs, and the results have contributed to dissemination of knowledge through each society. We propose to assess whether publication of the Guidelines has led to strengthening of the measures adopted to prevent occupational exposure.

The ONS revision member MiKaeka Olsen MS, APRN-CNS, and AOCNS stated that there was a consideration of USP Chapter 800 which was issued in 2016 and builds upon guidance from ONS, ASHP, OSHA, and NIOSH. It is the most current and most stringent of the authoritative guidelines on the safe handling of chemotherapy drugs. Furthermore, in 2017, NIOSH plans to release a Current Intelligence Bulletin on reproductive risks associated with exposure to HD exposures and in 2018, plans to release an update of the 2004 Alert on HD. Influenced by such a movement, a key task will be to revise and reissue the Guidelines within 3 years in Japan.

Acknowledgments

We would like to thank the JSMO President, Dr. Yuichiro Ohe, the JASPO President, Dr. Kazushi Endo, and members of the Expert Committee, Assessment Committee, and Cooperation Committee for guiding us through the publication of the Guideline.

Financial support and sponsorship

This study was supported by grants of Japanese Society of Cancer Nursing (JSCN), Japanese Society of Medical Oncology (JSMO), and Japanese Society of Pharmaceutical Oncology (JASPO).

Conflicts of interest

There are no conflicts of interest.

References

1. Miyuki S, Setsuko A, Hiromasa I, Chika F, Shigefumi M, Sumiyo I, et al. 7th Scientific Subcommittee, Japanese Society of Hospital Pharmacists, 2013. Research and investigation for the development of guidelines for safe handling of anticancer drugs (Final Report). Jpn Soc Hosp Pharm 2014;50:1065-71.
2. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990;47:1033-49.
3. International Society of Oncology Pharmacy Practitioners Standards Committee ISOPP standards of practice. Safe handling of cytotoxics. J Oncol Pharm Pract 2007;13 Suppl:1-81.
4. Polovich M. Safe Handling of Hazardous Drugs. 2nd ed. Pittsburgh, PA: Oncology Nursing Society; 2011. p. 19-20.
5. JSCN/JSMO/JASPO Joint Guidelines for Safe Handling of Cancer Chemotherapy Drugs. Kanehara Co., Ltd.; 2015. p. 7. (in Japanese)
6. JSCN/JSMO/JASPO Joint Guidelines for Safe Handling of Cancer Chemotherapy Drugs. Vol. 1. Kanehara Co., Ltd.; 2015. p. 25-26, 41-42,62-63. (in Japanese)
7. Selevan SG, Lindbohm M-L, Hornung RW, Hemminki K. A study of occupa tional exposure to antineoplastic drugs and fetal loss in nurses. N Engl J Med 1985;313(19): 1173-1178.
8. Stücker I, Caillard J-F, Collin R, Gout M, Poyen D, Hémon D. Risk of spontaneous abortion among nurses handling antineoplastic drugs. Scand J Work Environ Health 1990;16:102–107.
9. Hemminki K, Kyrönen P, Lindbohm M-L. Spontaneous abortions and malfor mations in the offspring of nurses exposed to anesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. J Épi demiol Commun Health 1990;39:141–147.
10. Peelen S, Roeleveld N, Heederik D, Krom hout H, de Kort W. Toxic effects on reproduction in hospital personnel. Reproductie-toxische effecten bij ziekenhuispersoneel. Netherlands: Elsevier. 1999 (in Dutch).
11. Valanis B, Vollmer WM, Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and still births among nurses and pharmacists. J Occup Environ Med 1999;41(8):632–638.
12. National Institute for Occupational Safety and Health. Preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. Retrieved from http://www.cdc.gov/niosh/docs/2004-165/; 2004. p. 6.
13. Dranitsaris G, Johnston M, Poirier S, Schueller T, Milliken D, Green E, et al. Are health care providers who work with cancer drugs at an increased risk for toxic events? A systematic review and meta-analysis of the literature. J Oncol Pharm Pract 2005;11:69-78.
14. Polovich M. Safe Handling of Hazardous Drugs. 2nd ed. Pittsburgh, PA: Oncology Nursing Society; 2011. p. 5-11.
15. Skov T, Maarup B, Olsen J, Rørth M, Winthereik H, Lyng E. Leukaemia and reproductive outcome among nurses working with antineoplastic agents: self-reported miscarriages and still births among nurses and pharmacists. J Occup Environ Med 1999;41(8):632–638.
16. Polovich M. Safe Handling of Hazardous Drugs. 2nd ed. Pittsburgh, PA: Oncology Nursing Society; 2011. p. 5-11.
17. Fransman W, Roeleveld N, Peelen S, de Kort W, Kromhout H,
Heederik D. Nurses with dermal exposure to antineoplastic drugs: Reproductive outcomes. Epidemiology 2007;18:112-9.

18. Quansah R, Jaakkola JJ. Occupational exposures and adverse pregnancy outcomes among nurses: A systematic review and meta-analysis. J Womens Health (Larchmt) 2010;19:1851-62.

19. Lawson CC, Rocheleau CM, Whelan EA, Livedoti Hibert EN, Grajewski B, Spiegelman D, et al. Occupational exposures among nurses and risk of spontaneous abortion. Am J Obstet Gynecol 2012;206:327.e1-8.

20. Sessink PJ, Trahan J, Coyne JW. Reduction in Surface Contamination With Cyclophosphamide in 30 US Hospital Pharmacies Following Implementation of a Closed-System Drug Transfer Device. Hosp Pharm 2013;48:204-12.

21. Sessink PJ, Connor TH, Jorgenson JA, Tyler TG. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. J Oncol Pharm Pract 2011;17:39-48.

22. Favier B, Labrosse H, Gilles-Afchain L, Crozet C, Perol D, Chaumard N, et al. The Phaseal® system: Impact of its use on workplace contamination and duration of chemotherapy preparation. J Oncol Pharm Pract 2012;18:37-45.

23. Yoshida J, Tei G, Mochizuki C, Masu Y, Koda S, Kumagai S. Use of a closed system device to reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment. Ann Occup Hyg 2009;53:153-60.

24. Wick C, Slawson MH, Jorgenson JA, Tyler LS. Using a closed-system protective device to reduce personnel exposure to antineoplastic agents. Am J Health Syst Pharm 2003;60:2314-20.

25. De Ausen L, DeFreitas EF, Littleton L, Lustik M. Leakage from closed-system transfer devices as detected by a radioactive tracer. Am J Health Syst Pharm 2013;70:619-23.

26. Nishigaki R, Konno E, Sugiyasu M, Yonemura M, Otsuka T, Watanabe Y. The usefulness of a closed-system device for the mixing of injections to prevent occupational exposure to anticancer drugs. J Jpn Soc Hosp Pharm 2010;46:113-7. (in Japanese).

27. Sato J, Mori M, Kumagai M, Nakayama S, Yamauchi S, Kudo K, et al. The usefulness of a closed preparation system, Chemosafe®, for anticancer drugs. J Jpn Soc Hosp Pharm 2012;48:441-4. (in Japanese).

28. Hama K, Hiramatake M, Nakanishi S, Tanaka S, Hashida T. The evaluation of comprehensive countermeasures to reduce occupational exposure to anticancer drugs during preparation and administration. Jpn J Pharm Health Care Sci 2013;39:700-10. (in Japanese).

29. Teruii K, Okajima H, Nakajima Y. Safety evaluation of new anticancer chemotherapy administration system – Compared to the results from a former study. Jpn J Cancer Chemother 2011;38:1483-7 (in Japanese).

30. Villarini M, Dominici L, Piccinini R, Fatigoni C, Ambrogi M, Curti G, et al. Assessment of primary, oxidative and excision repaired DNA damage in hospital personnel handling antineoplastic drugs. Mutagenesis 2011;26:359-69.

31. Undeger U, Basaran N, Kara A, Guc D. Assessment of DNA damage in nurses handling antineoplastic drugs by the alkaline COMET assay. Mutat Res 1999;439:277-85.

32. JSCN/JSMO/JASPO Joint Guidelines for Safe Handling of Cancer Chemotherapy Drugs. Kanehara Co., Ltd.; 2015. p. 45. (in Japanese).