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Field Study

Actual Conditions of the Mixing of Antineoplastic Drugs for Injection in Hospitals in Osaka Prefecture, Japan

Jin YOSHIDA[1], Hiroshi KOSAKA[1], Shozo NISHIDA[2] and Shinji KUMAGAI[1]

[1]Department of Environmental Health, Osaka Prefectural Institute of Public Health and [2]Division of Pharmacotherapy, Kinki University School of Pharmacy, Japan

Abstract: Actual Conditions of the Mixing of Antineoplastic Drugs for Injection in Hospitals in Osaka Prefecture, Japan: Jin YOSHIDA, *et al.* Department of Environmental Health, Osaka Prefectural Institute of Public Health—We conducted a questionnaire survey in order to grasp the actual conditions under which antineoplastic drugs are mixed for injection in hospitals. Questionnaires were sent to all 155 hospitals with 100 or more beds for general patients in Osaka Prefecture, Japan. The response rate was 69.0%. Mixing of antineoplastic drugs was done in 81.3% of the hospitals. The questionnaire was answered by doctors in 17.2% of the hospitals with antineoplastic drugs, nurses in 11.5%, and pharmacists in 70.1%. Mixing of antineoplastic drugs was done by doctors in 58.6% of the hospitals, nurses in 44.8%, and pharmacists in 63.2% (multiple answers). Occupational exposure to antineoplastic drugs was recognized in 97.7% of the hospitals. The mean frequency of the mixing operation was 8.8 d per month per worker. The mean number of antineoplastic drugs handled was 7.4 types. Guidelines for the safe handling of antineoplastic drugs were used in 52.8% of the hospitals and a biological safety cabinet was available in 57.4%. Gloves, mask, gown and goggles were used in 82.7, 69.0, 62.1 and 36.8% of the hospitals, respectively, but no personal protective equipment was used in 10.1%. The safety precautions of the hospitals in which the number of beds was small tended to be fewer than those of the hospitals in which the number of beds was large. Used vials and ampoules were disposed of as clinical, infectious or exclusive antineoplastic drug waste by 74.7% of the hospitals. Safety measures for handling the excrement of patients treated with antineoplastic drugs were performed in 8.0% of the hospitals. In 43.7% of the hospitals, the responders had experienced accidents during antineoplastic drug preparation, such as drugs adhering to hands or eyes, drug leakage, accidental injection and cutting by ampoules. Because of the adverse effects of antineoplastic drugs, all hospitals in which the healthcare workers handle them should promote safety precautions.
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Key words: Antineoplastic drugs, Healthcare worker, Hospital, Safety precautions

Antineoplastic drugs are clearly beneficial for patients but there is concern about the health risk to healthcare workers handling them[1)]. Usually, antineoplastic drugs are mixed and diluted as infusions by health care workers, then administered to patients. In these processes, the air, workbenches, clothes, medical equipment used and excrement of the patients may be contaminated by the antineoplastic drugs[2)]. Healthcare workers are exposed to antineoplastic drugs via inhalation, skin contact, eye contact and oral ingestion[2)]. Some antineoplastic drugs are known to induce cytotoxicity, genotoxicity and carcinogenicity[3, 4)]. Increases in hair loss, skin rash, infertility, miscarriage, birth defects, chromosomal aberrations, sister chromatid exchanges, and DNA strand break have been observed among healthcare workers handling antineoplastic drugs[2, 5–11)].

Guidelines for safe handling of antineoplastic drugs were formulated in 1981, 1981, 1983 and 1990 in Australia, Canada, England, and America, respectively[12–15)]. In Japan, guidelines for handling antineoplastic drugs in the hospital were issued by the Japan Pharmaceutical Association in 1991[16)]. However, the extent of the implementation of these guidelines is unknown. Ishii et al. reported that in a survey of 313 hospitals in Japan in 2001, 40% of the nurses were not aware of the potential adverse effects of occupational exposure to antineoplastic drugs[17)]. In 2004, we investigated the genotoxic risks of nurses handling antineoplastic drugs in Japan. We found that the nurses

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Correspondence to: J. Yoshida, Department of Environmental Health, Osaka Prefectural Institute of Public Health, 1–3–69, Nakamichi, Higashinari-ku, Osaka 537-0025, Japan (e-mail: jnyosida@iph.pref.osaka.jp)

had been exposed to these drugs and suggested that lymphocyte DNA damage could had been induced by such drugs[18]. In the present study, we conducted a questionnaire survey in order to identify the conditions under which antineoplastic drugs are mixed in hospitals.

Methods

All 155 hospitals with 100 or more beds for general patients in Osaka Prefecture as of April 2006 were selected for the questionnaire survey. Two types of questionnaire were used. One asked about the occurrence of mixing operations and job descriptions related to them. The other questionnaire asked for details on the conditions of the mixing operations, including their frequency, types of antineoplastic drugs handled, awareness of occupational exposure to antineoplastic drugs, the need for systematic education on the mixing of antineoplastic drugs, health concerns due to exposure to antineoplastic drugs, implementation of guidelines, the existence of biological safety cabinets and workbenches dedicated to the handling of antineoplastic drugs, the use of personal protective equipment, the use of sterilized sheets and spill kits, the adoption of techniques to retain negative pressure in the vial, the disposal procedures of clinical waste related to antineoplastic drug use and the excrement of patients treated with antineoplastic drugs, and the occurrence of accidents during the mixing operation. These questionnaires were sent to the hospitals in July 2006 and responses were received from August to October 2006.

Of the 155 hospitals, 107 responded to our questionnaire (69.0%). Antineoplastic drugs were mixed in 87 of the 107 hospitals (81.3%). The questionnaires were answered by doctors in 17.2% of the hospitals, nurses in 11.5%, and pharmacists in 70.1%. In the present study, the median number of beds in the 87 hospitals in which antineoplastic drugs were handled was 332. Hospitals with less than 332 beds and those with 332 or more beds were classified as small-scale and large-scale, respectively. Comparison of the mean values of the two groups was conducted using the t test. Comparison of the percentages of the two groups was conducted using Fisher's exact test. These calculations were conducted using SPSS 12.0 J software (SPSS Japan Inc, Japan).

Results

Job description, frequency of mixing operation and frequency of handling antineoplastic drugs

The antineoplastic drugs were mixed by doctors in 58.6% of the hospitals, nurses in 44.8%, and pharmacists in 63.2% (multiple answers).

The mean frequency of the mixing operation was 8.8 (0.5–25) d per month per worker. The mean frequencies in small- and large-scale hospitals were 8.5 and 9.0 days per month per worker, respectively, with the difference not being significant.

Table 1. Antineoplastic drugs handled in 5 or more hospitals

Antineoplastic drug	Number (%)
Paclitaxel	63 (72.4)
Fluorouracil	61 (70.1)
Cisplatin	51 (58.6)
Irinotecan	51 (58.6)
Gemcitabine	39 (44.8)
Docetaxel	37 (42.5)
Cyclophosphamide	36 (41.4)
Epirubicin	36 (41.4)
Carboplatin	27 (31.0)
Oxaliplatin	24 (27.6)
Doxorubicin	24 (27.6)
Trastuzumab	23 (26.4)
Vinorelbine	17 (19.5)
Rituximab	12 (13.8)
Methotrexate	11 (12.6)
Vincristine	11 (12.6)
Etoposide	9 (10.3)
Nedaplatin	7 (8.0)
MitomycinC	6 (6.9)
Vinblastine	5 (5.7)
Vinorelbine	5 (5.7)

The mean number of antineoplastic drugs handled was 7.4 (1–18) types excluding the response "using almost all antineoplastic drugs" (n=1). Table 1 lists the antineoplastic drugs used in 5 or more hospitals. The mean number of antineoplastic drugs used was 6.1 and 8.8 types, respectively, for small- and large-scale hospitals, with the difference being significant (p=0.002).

Awareness of occupational exposure to antineoplastic drugs

Occupational exposure to antineoplastic drugs was recognized in 97.7% of the hospitals. The need for systematic education on the mixing of antineoplastic drugs was recognized in 93.1% of the hospitals. In 88.5% of the hospitals, the respondents felt concern about the adverse effects on their own health due to exposure to antineoplastic drugs. When the answers were classified by job description, occupational exposure to antineoplastic drugs was recognized by 86.7% of the doctors, 90.0% of the nurses and 100% of the pharmacists. The need for systematic education on the mixing of antineoplastic drugs was recognized by 86.7% of the doctors, 100% of the nurses and 95.1% of the pharmacists. Among the doctors, nurses and the pharmacists, respectively 66.7%, 90.0% and 95.1% of the respondents felt concern about adverse effects on their own health

Table 2. Proportions of hospitals using safety precautions

Safety precautions	Number (%)			*p* value[c]
	Total (n=87)	Small-scale hospitals[a] (n=44)	Large-scale hospitals[b] (n=43)	
Safety facilities				
Use of guidelines for safe handling of antineoplastic drugs	46 (52.8)	16 (36.3)	30 (69.8)	0.005
Installation of biological safety cabinet	50 (57.4)	15 (34.1)	35 (81.4)	<0.001
Use of workbench only for handling antineoplastic drugs	39 (44.8)	12 (27.3)	27 (62.7)	0.002
Personal protective equipment				
Gloves	72 (82.7)	33 (75.0)	39 (90.7)	0.142
Mask	60 (69.0)	27 (61.4)	33 (76.7)	0.240
Gown	54 (62.1)	22 (50.0)	32 (74.4)	0.044
Goggles	32 (36.8)	16 (36.4)	16 (37.2)	1.000
Safety equipment				
Sterilized sheet	50 (57.5)	19 (43.2)	31 (72.1)	0.016
Spill kit	19 (21.8)	8 (18.2)	11 (25.6)	0.603
Technique				
Technique to retain negative pressure in vial	66 (75.9)	27 (61.4)	39 (90.7)	0.009

[a] Number of beds for general patients is less than 332. [b] Number of beds for general patients is 332 or more. [c] Comparison of the percentages between small-scale and large-scale hospitals by Fisher's exact test.

from exposure to antineoplastic drugs. In the present study, we did not compare the awareness of occupational exposure to antineoplastic drugs with job description by statistical test, because the sample number was not large enough.

Safety precautions

The status of safety precautions related to the mixing operation is given in Table 2. The percentages of use of guidelines were significantly (p=0.005) lower in small-scale hospitals than in than large-scale hospitals. Also, the percentages of installation of biological safety cabinets were significantly (p<0.001) lower in small-scale hospitals than in large-scale hospitals. A ventilation fan only had been installed in 21.3% of the hospitals, and neither cabinet nor fan in 21.3%.

The mixing operation was done on a workbench dedicated to the handling of antineoplastic drugs in 44.8% of the hospitals. The percentages of exclusive-use workbenches were significantly (p=0.002) lower in small-scale hospitals than in large-scale hospitals, and the percentages of exclusive-use workbenches were 72.0 and 8.8%, respectively, for hospitals with and without a biological safety cabinet (p<0.001, Fisher's exact test). In 48.3% of the hospitals, non-antineoplastic drugs were also handled on the workbench for handling antineoplastic drugs, and in 6.9% of the hospitals, even office work was done on the same workbench.

Gloves, mask, gown and goggles were available in 82.7, 69.0, 62.1 and 36.8% of the hospitals, respectively. The percentages of gown equipment were significantly (p=0.044) lower in small-scale hospitals than in large-scale hospitals. In 29.2% of the hospitals in which gloves were used, they were worn doubly. No personal protective equipment was used in 10.1% of the hospitals.

To trap antineoplastic drug spill, a sterilized sheet made of absorbent material can be laid out on the workbench. A spill kit can also be used, consisting of gloves, mask, gown, goggles and a sterilized sheet to prevent contamination from antineoplastic drugs due to accidental spilling. A sterilized sheet and a spill kit were used in 57.5% and 21.8%, respectively, of the hospitals. The percentages of use of sterilized sheet were significantly (p=0.016) lower in small-scale hospitals than in large-scale hospitals. Sterilized sheets were used in 56.8% of the hospitals when workers wore a single pair of gloves, and in 90.4% of the hospitals when workers wore a double pair of gloves (p=0.006, Fisher's exact test).

In order to avoid the spread of antineoplastic drugs in the mixing operation, the vial should be kept under negative pressure[16]. A technique for doing this had been adopted by 75.9% of the hospitals. The percentages of implementation of this technique were significantly (p=0.009) lower in small-scale hospitals than in large-scale hospitals.

Disposal process of clinical waste from antineoplastic drug use and excrement of patients treated with antineoplastic drugs

Table 3 shows the status of the disposal process of

Table 3. Disposal procedures of used vials, ampoules and needles and excrement of patients treated with antineoplastic drugs (n=87)

Disposal procedure	Number (%)
Used vials and ampoules	
Clinical waste	49 (56.3)
Infectious waste	14 (16.1)
Waste only from antineoplastic drug use	2 (2.3)
Unburnable waste	17 (19.5)
Unknown	1 (1.1)
No answer	4 (4.6)
Used needles	
Clinical waste	64 (73.6)
Infectious waste	15 (17.2)
Waste only from antineoplastic drug use	2 (2.3)
Unburnable waste	0 (0.0)
Unknown	1 (1.1)
No answer	5 (5.7)
Excrement of patients treated with antineoplastic drugs	
Dispose with care and use protection equipment	7 (8.0)
Dispose as for general patients	69 (79.3)
Unknown	2 (2.3)
No answer	9 (10.3)

clinical waste from antineoplastic drug use and excrement of patients treated with antineoplastic drugs. Used vials and ampoules were disposed of as clinical waste by 56.3% of the hospitals, infectious waste by 16.1%, exclusive waste for antineoplastic drugs by 2.3%, and unburnable waste by 19.5%. Used needles were disposed of as clinical waste by 73.6% of the hospitals, infectious wastes by 17.2%, and exclusive waste for antineoplastic drugs by 2.3%. Safety measures for handling excrement of patients treated with antineoplastic drugs were performed by 8.0% of the hospitals, while it was disposed of as for general patients by 79.3% of the hospitals.

Accidents during the mixing operation

In 43.7% of the hospitals, the respondents had experienced accidents during antineoplastic drug preparation, including the drugs adhering to hands or eyes, drug leakage, accidental injection and cutting by ampoules.

Discussion

We conducted a questionnaire survey in order to identify the conditions under which antineoplastic drugs are mixed in hospitals in Osaka Prefecture. Mixing of antineoplastic drugs was done in 81.3% of the hospitals. It seems to be a routine procedure in general hospitals, not being limited to university hospitals or specialist cancer chemotherapy centers.

Ishii *et al*. reported that the mixing of antineoplastic drugs was done by doctors in 29.9% of the hospitals surveyed in 2000, by nurses in 55.2%, and by pharmacists in 0.7%[17]. In the present study, the antineoplastic drugs were mixed by doctors in 58.6% of the hospitals, nurses in 44.8%, and pharmacists in 63.2%, with an increase in the rate of pharmacists over the past 6 yr. One factor has been the revision of the medical treatment fee under which a national insurance point is now added when pharmacists mix antineoplastic drugs.

The mean frequency of the mixing operation was 8.8 d per month per worker, with no difference being observed between small- and large-scale hospitals. Consequently, the possibility of exposure to antineoplastic drugs did not seem to depend on the scale of the hospital. In the present study, we asked about the frequency of the mixing operation, not the amount of antineoplastic drugs handled. As many kinds of antineoplastic drugs were used in the hospitals and their toxicity evaluation varied, we could not adopt a standard representation of the amount handled. The mean number of antineoplastic drugs handled was 7.4 types, with large-scale hospitals handling more types than small-scale ones. The number of types of antineoplastic drugs seemed to depend on the scale of the hospital.

Most respondents were aware of the occupational exposure to antineoplastic drugs. We did not compare awareness of occupational exposure to antineoplastic drugs with job description, because the sample number was not large enough. Awareness of antineoplastic drugs may differ with job description, further studies are necessary.

Guidelines for the safe handling of antineoplastic drugs had been adopted by 52.8% of the hospitals surveyed, with the rate being higher for large-scale hospitals than small-scale ones. Ishii et al. reported that 9.8% of the hospitals had adopted guidelines within the prior six years[17]. Biological safety cabinets had been installed in 57.4% of the hospitals, with more being found in large-scale hospitals than in small-scale hospitals. The mixing of non-antineoplastic drugs or usual office work was done on the workbench for handling antineoplastic drugs in 91.2% of the hospitals which had not installed a biological safety cabinet. Studies have reported that workbenches for handling antineoplastic drugs were contaminated by antineoplastic drugs[18–20]. Conducting the mixing of non-antineoplastic drugs or office work on a workbench used for handling antineoplastic drugs was likely to lead to contamination of other patients and health care workers. We recommend that the workbench for mixing antineoplastic drugs be separated from the space used by other health care workers.

The results related to protective equipment for personal wear, such as gloves, mask, gown and goggles, revealed that goggles were not used in more than 60% of the

hospitals. With respect to gloves, as some antineoplastic drugs have been reported to permeate through them, wearing double gloves and changing them within a specified time (30 to 60 min) are recommended[2, 16, 21]. In some guidelines, using sterilized sheets and a spill kit are recommended[2, 16]. In 29.2% of the hospitals using gloves, they were worn doubly, and sterilized sheets were used in 90.4% of these hospitals. These hospitals abided by the guidelines, indicating strong interest in the safe handling of antineoplastic drugs. In the present study, the lowest percentage of use was recorded for goggles. Ben-Ami *et al*. reported that health care workers felt awkward wearing goggles[22]. We observed similar results in our present study. However, as our study revealed a risk of antineoplastic drugs entering the eyes, the use of goggles should be promoted. In 10.1% of the hospitals, personal protective equipment was not used. As the hands or gloves of health care workers who handle antineoplastic drugs have been reported to be contaminated by antineoplastic drugs, all workers handling antineoplastic drugs should wear suitable personal protective equipment[19, 20].

The technique of retaining negative pressure in the vial was being used in 75.9% of the hospitals. Many healthcare workers seemed to use this technique, even though special training is needed to master it.

Occupational exposure to antineoplastic drugs and its risk were recognized as a health risk in 97.7% of the hospitals, but implementation of safety precautions for handling antineoplastic drugs had been adopted in greater measure by the large-scale hospitals. Because the mixing operation of antineoplastic drugs was done in 81.3% of the hospitals surveyed and there is no significant difference in the mean frequencies between small- and large-scale hospitals, safety precautions must be adopted by all hospitals.

Used vials and ampoules were disposed of as unburnable wastes by 19.5% of the hospitals. As used vials, ampoules, syringes and personal protective equipment can be contaminated by antineoplastic drugs, they should be disposed of in exclusive waste containers. Proper treatment of this waste will protect healthcare workers and cleaners from antineoplastic drug contamination. The safety measures related to the handling of excrement of patients treated with antineoplastic drugs were not used by many of the hospitals. This can be problematic as many antineoplastic drugs are excreted in the urine and/or feces; up to 25% of cyclophosphamide administered is excreted in urine as the unchanged substance for 24 h[23]. The excrement of patients treated with antineoplastic drugs within 48 h should be handled with protection equipment[2]. Methods of handling patient excrement are not described in the guidelines issued by the Japan Pharmaceutical Association, and need to be established.

In 43.7% of the hospitals, the respondents had experienced accidents during antineoplastic drug preparation. As countermeasures against many of the accidents reported in our survey are listed in the guidelines, promoting understanding of these guidelines should aid in their prevention[16]. A further problem arises with ampoules, which can cause cutting and can lead to the vaporization of residual drugs. Pharmaceutical companies should replace the ampoule form with a safer type of container.

Conclusions

The mixing operation of antineoplastic drugs was found to be a common practice in the hospitals surveyed, and most respondents recognized the possibility of occupational exposure to antineoplastic drugs and its risks. The percentages of hospital staff participating in the mixing operation were about the same for doctors, nurses and pharmacists. Guidelines and a biological safety cabinet were in use in about half of the hospitals, and personal protective equipment, with the exception of goggles, were used in many hospitals. In small-scale hospitals, the adoption of many of the safety precautions had not been implemented. Most hospitals did not employ safety measures for handling the excrement of patients treated with antineoplastic drugs. Further consideration of the safety guidelines regarding the handling of antineoplastic drugs and their stricter implementation are strongly recommended.

References

1) Sorsa M, Hemminki K and Vainio H: Occupational exposure to anticancer drug—potential and real hazards. Mutat Res 154, 135–149 (1985)
2) National Institute for Occupational Safety and Health (NIOSH). NIOSH ARERT Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings. Cincinnati: NIOSH, 2004: 1–61.
3) International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 26: Some Antineoplastic and Immunosuppressive Agents. Lyon: IARC, 1981.
4) International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 76: Some Antiviral and Antineoplastic Drugs, and Other Pharmaceutical Agents. Lyon: IARC, 2000.
5) Valanis B, Vollmer WM and Steele P: Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. J Occup Environ Med 41, 632–638 (1999)
6) Krstev S, Perunicic B and Vidakovic A: Work practice and some adverse health effects in nurses handling antineoplastic drugs. Med Lav 94, 432–439 (2003)
7) Falck K, Grohn P, Sorsa M, Vainio H, Heinonen E and Holsti LR: Mutagenicity in urine of nurses handling

cytostatic drugs. Lancet 1, 1250–1251 (1979)
8) Thiringer G, Granung G, Holmen A, Hogstedt B, Jarvholm B, Jonsson D, Persson L, Wahlstrom J and Westin J: Comparison of methods for the biomonitoring of nurses handling antitumor drugs. Scand J Work Environ Health 17, 133–138 (1991)
9) Burgaz S, Karahalil B, Canhi Z, Terzioglu F, Ancel G, Anzion RB, Bos RP and Huttner E: Assessment of genotoxic damage in nurses occupationally exposed to antineoplastics by the analysis of chromosomal aberrations. Hum Exp Toxicol 21, 129–135 (2002)
10) Jakab MG, Major J and Tompa A: Follow-up genotoxicological monitoring of nurses handling antineoplastic drugs. J Toxicol Environ Health A 62, 307–318 (2001)
11) Undeger U, Basaran N, Kars A and Guc D: Assessment of DNA damage in nurses handling antineoplastic drugs by the alkaline COMET assay. Mutat Res 439, 277–285 (1999)
12) The Society of Hospital Pharmacists of Australia: Guidelines of safe handling of cytotoxic drugs in pharmacy departments and hospital wards. Hospital Pharm 16, 17–20 (1981)
13) Canadian Society of Hospital Pharmacists: Guidelines for the handling of hazardous pharmaceuticals. Can J Hosp Pharm 34, 126–128 (1981)
14) Working party report: Guidelines for handling of cytotoxic drugs. Pharm J, 230 (1983)
15) American Society of Health-System Pharmacists (ASHP): ASHP technical assistance bulletin on handling cytotoxic drugs in hospitals. Am J Hosp Pharm 42, 131–137 (1985)
16) Kitada M, Morikawa A, Katou H and Nakayama S. The revised version of guideline of handling antineoplastic drugs in medical center —Manual of handling antineoplastic drugs. Tokyo: Jiho Co, 2005.
17) Ishii N, Dakeishi M, Sasaki M and Murata K: Safety awareness of anticancer drug handling among Japanese nurses. Jpn J Public Health 52, 727–735 (2005)
18) Yoshida J, Kosaka H, Tomioka K and Kumagai S: Genotoxic risks to nurses from contamination of the work environment with antineoplastic drugs in Japan. J Occup Health 48, 517–522 (2006)
19) Sessink PJ, Anzion RB, Van den Broek PH and Bos RP: Detection of contamination with antineoplastic agents in a hospital pharmacy department. Pharm Weekbl Sci 14, 16–22 (1992)
20) Connor TH, Anderson RW, Sessink PJ, Broadfield L and Power LA: Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. Am J Health Syst Pharm 56, 1427–1432 (1999)
21) Wallemacq PE, Capron A, Vanbinst R, Boeckmans E, Gillard J and Favier B: Permeability of 13 different gloves to 13 cytotoxic agents under controlled dynamic conditions. Am J Health Syst Pharm 63, 547–556 (2006)
22) Ben-Ami S, Shaham J, Rabin S, Melzer A and Ribak J: The influence of nurses' knowledge, attitudes, and health beliefs on their safe behavior with cytotoxic drugs in Israel. Cancer Nurs 24, 192–200 (2001)
23) Fujita H. Alkylating agents (section 2), Pharmacokinetics of Antineoplastic drugs. Osaka: Medical Review Co. Ltd., 1986: 9–22.