High risk of hazardous drug exposure in the caregivers of pediatric cancer

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Cytotoxic agents are the major part of current therapeutic arsenal in pediatric oncology. Recently, small molecules have been combined in the standard regimen for targeted cancer therapy. Both drugs provoke adverse effects on the living cells via the specific and non-specific actions to neoplastic cells. Considering genetic and epigenetic events, the late effect rather than acute toxicity is a matter of concern for healthy subjects at risk of exposure to anticancer drugs. To reduce the risk, a list of hazardous drugs (HDs) has been updated by the National Institute for Occupational Safety and Health (NIOSH) including commonly used cytotoxic agents. HDs are defined by their association with genotoxicity, carcinogenicity, teratogenicity, impaired fertility, reproductive toxicity, and/or serious organ toxicity even at a lower dose.[1] The American Society of Clinical Oncology (ASCO) standard promotes the safety of professional staff of pharmacists, physicians, nurses, and other collaborators in oncology care.[2] It recommends the preventive measures to avoid the toxic products, incorporating the latest evidence of the deleterious late effects after exposure, and the benefits of control measures, along with expert consensus. United States Pharmacopeia Chapter <800> requires an appropriate list of HDs in healthcare settings, providing concrete information regarding the articles of personal protective equipment, as well as where and how they should be donned, used, and removed is prescribed.[3]

Several guidelines for the occupational exposure to HDs have been established for the health of hospital workers,[1-5] but not the family members of childhood cancer. We thus investigated the exposure of caregiver and medical staff to anticancer drugs and the environmental contamination. Fifteen inpatients with pediatric cancer were recruited who received high-dose cyclophosphamide (CPM) from 2017 to 2018. Seven infants and 8 adolescents had 4 leukemias and 11 solid tumors. The median age at the time of this study was 78 months ranging from 13 to 200 months. The infants and adolescents received CPM of 1g /m^2 or more; median 640 (range 620~1300) mg, and 1230 (range 780~1230) mg, respectively. Six hours after the first administration, the concentration of CPM was measured in the urine and saliva from attending mothers, nurses, doctors, nursery teachers, child-life specialists, and housekeeping staff members in the ward, using the liquid chromatography/mass spectrometry method (Shionogi Analysis Centre Co., Ltd., Osaka, Japan)[6]. Safe handling and closed-system-drug-transfer devices (JMS Co. Ltd., Hiroshima, Japan) are the standard of our center to minimize the technical exposure.[7] This study was approved by the institutional review board of Kyushu University. Five of 7 (71%) infant's and 2 of 8 (25%) adolescent's mothers showed increased urine levels of CPM. The median value of infant's mothers (192 ng/10 mL, range 0~1,510) was significantly higher than that of adolescent's mothers (0 ng/10 mL, 0~58.4) (p =0.005). CPM was detected in the saliva samples of two mothers caring infants, but not in the urine or saliva of any medical staff (**Figure**). The

environmental contamination in a room of the infant whose mother showed the highest concentrations was assessed by the modified method.[6] High levels of CPM were determined in the monitoring samples from a 17-year-old boy; toilet floor (1020 times of the detection limit), toilet seat (167 times), wash basin (45.6 times), a 13-year-boy; underwear (735 times) bed sheets (224 times), bed fence (34.8 times), bedside floor (20.9 times), exhaust vent (13.1 times), bedside table (7.4 times), door knob (4.9 times), curtain (4.7 times), and a 2-year-boy; bathing hot water (205 times) at 24 hours after the first administration, respectively. No staff having detectable CPM levels represented the control of HDs exposure in our hospital. In contrast, the exposure was frequently found in attending mothers caring infants. The higher levels of CPM in infants' mothers than in adolescents' mothers are explained by the closer contact for care. The environmental contamination has occurred from the body fluid of patients but not the drug delivery.

The latest systems and guidelines have effectively controlled the accidental exposures of drugs to medical staff, as shown in the present results, throughout the process from the formulation in the pharmacy department, transportation, and administration to bed-side patients. The mother's exposure is categorized as an intermediate risk. It may occur in case of high-dose therapy with limited duration. However, the metabolites of CPM including 4-hydroxycyclophosphamide show cytotoxicity.[9] The mixture of selected cytostatic drugs has an augmented cytotoxicity leading to the late effects on genome even at low concentrations.[10] During the long-term intense chemotherapy for pediatric cancer, the preliminary results may raise the need for preventive measures for caregivers according to the equivalent levels to medical staffs.

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Ethics approval and consent to participate

This study was certified by the Institutional Review Board of Kyushu University (No.20192015).

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Contributors' Statements

YN, YK, and SO were the principal investigators and take primary responsibility for the paper. UO and YH performed the clinical management with helpful discussion regarding the completion of the work. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Abbreviations	Abbreviations
HDs	hazardous drugs
NIOSH	National Institute for Occupational Safety and Health
ASCO	American Society of Clinical Oncology
CPM	cyclophosphamide

References

1. Connor TH, MacKenzie BA, DeBord DG, et al. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016, Publication Number 2016-161 (Supersedes 2014-138). OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH), 2016
2. Celano P, Fausel CA, Kennedy EB, et al. Safe handling of hazardous drugs: ASCO standards. J Clin Oncol 2019;37: 598–609.

3. US Pharmacopeia. General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings
4. Polovich M, Olsen M. Safe handling of hazardous drugs. 3rd Ed. Oncology Nursing Society, 2018
5. Dillon LR. Quality control: personal protective equipment for use when handling hazardous drugs. Int J Pharm Compd 2020; 24:30–36.
6. Makino T, Hasegawa N, Takizawa R, et al. Suggestions for Protecting Breast Cancer Patients Receiving Outpatient Chemotherapy and Their Families Against the Exposure Risk from Salivary Cyclophosphamide. Int J Nurs Clin Pract 2020;7: 320, doi: https://doi.org/10.15344/2394- 4978/2020/320
7. Gourd E. New drug-transfer device reduces hazardous exposure. Lancet Oncol 2017;18: e312.
8. Voelcker G. Causes and possibilities to circumvent cyclophosphamide toxicity. Anticancer Drugs doi: 10.1097/CAD.0000000000000912, 2020 Feb 8
9. Gajski G, Ladeira C, Gerić M, et al. Genotoxicity assessment of a selected cytostatic drug mixture in human lymphocytes: A study based on concentrations relevant for occupational exposure. Environ Res 2018;161: 26–34.
10. Sessink PJ. Environmental contamination with cytostatic drugs: past, present and future. Saf Consid Oncol Pharm Special Edition 2011

Figure legends

Figure. CPM concentration in urine (A) and saliva (B) in family caregivers and healthcare professionals. We administered high-dose CPM to 15 hospitalized pediatric cancer patients, and analyzed the concentration of CPM in the urine (U) and saliva (S) of mothers attending the patients (U=15, S =3), nurses (U, S=each 12), doctors (U, S=each 3), nursery teachers and child-life specialists (U, S=each 3), and housekeeping staff in the pediatric ward (U, S=each 3) by the liquid chromatography / mass spectrometry method (Shionogi Analysis Centre Co., Ltd., Osaka, Japan) on day 1 of chemotherapy. All samples were collected approximately 6 h after CPM administration to patients. The bars in each scatter diagram show the median values.