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Microbiological Risk Assessment in an Italian Oncology Pharmacy

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Abstract

Purpose: To perform a risk analysis of the microbiological features of cancer drug preparation and to propose control measures and corrective actions to improve these processes.

Summary: A multidisciplinary team was set up to assess cancer chemotherapy preparation. The team drew up a list of all the oncological preparations made in the Oncology Pharmacy Laboratory of our institute in 2017 and calculated their risk. The team then identified the risk-reducing factors that had been applied for the different preparations and finally reviewed the risk level of the preparations based on this reduction.

It emerged that 37,830 sterile injectable preparations were made in 2017 and 21,474 met environmental class requirements. The present analysis focused on the remaining 16,356 preparations.

Conclusion: Of the 37,830 oncological preparations made in our institute in 2017, only 12 (0.1%) did not fulfil SIFO technical standards with regard to their preparation. None of the 12 preparations involved an experimental drug.

Keywords: Microbiological risk; Anti-cancer drugs; Risk analysis; Quality management

Introduction

The handling of anticancer drugs carries a risk of toxicity for physicians, nurses, pharmacists and laboratory technicians [1-8]. It is thus recommended to centralize preparation in an oncology pharmacy laboratory to limit occupational exposure to these agents [9-11]. However, the preparation of anti-cancer drugs is a complex process and non-conformities may occur. Consequently, cancer drug compounding units are required to meet ever-increasing production standards and to respect good practice guidelines to ensure high product quality [12-14].

Our cancer institute (IRST IRCCS) has 36 inpatient beds, 30 beds in 3 Day Hospitals located within 30 km of each other, and a highly equipped and specialized central pharmacy (Oncology Pharmacy Unit). The pharmacy is in charge of compounding and dispensing cancer drugs. The aseptic preparation of antineoplastic drug products such as infusion bags, elastomeric pumps and ready-to-administer syringes is performed manually in Class II biological safety cabinets (BSC, Biotron, Budrio, Italy) and is fully-automated, with two robotic systems APOTECA chemo (Loccioni, Angeli di Rosora, Italy). Manual and robotic processes are run in 2 different Grade C cleanrooms. 37,830 antineoplastic therapies (2,302 of which for experimental drugs) were prepared in 2017 and 39,807 (2,701 of which for experimental drugs) in 2018, for a total of about 2,500 patients/year.

As part of the institute's policy for risk assessment and management of adverse events, a self-assessment questionnaire was administered to pharmacy staff in January 2018 to verify whether Italian pharmaceutical preparation norms (NBP FU XII, Norme di Buona Preparazione, versione FU XII), EU GMP guidelines (EU guidelines for good manufacturing practice medicinal products for human and veterinary use - annex 1 manufacture of sterile medicinal products of 25/11/2008) and technical standards of oncological pharmaceutics were respected. The outcome of the audit highlighted some areas worthy of attention, especially with regard to the microbiological safety of sterile injectable settings. Italian Society of Hospital Pharmacy (Società Italiana di Farmacia

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Ospedaliera - SIFO) technical standards are guidelines for oncology pharmacies and include all of the procedures, equipment and validation methods needed to guarantee the basic quality of galenical preparations. They were drawn up in 2017 by a SIFO Oncology Working Group in accordance with the regulations, guidelines and standards for magistral galenical preparations valid at the time of writing this paper. The main references for these standards are current pharmacopoeia and good preparation standards, GMPs, Italian ministerial recommendation no. 14 (Guidelines for the safety and health of workers exposed to antiblastic chemotherapy in the healthcare environment), international standards (QuapoS5, ISOPP, PIC/s 10-04), ISO standards and applicable national and European legislation.

SIFO technical standards specify that preparations with high microbiological risk must be performed in a class A environment with a class B background, whereas medium and low risk preparations can be made in a class A environment inserted in a class C background (Table 1). They also indicate that, in the absence of a microbiological risk assessment carried out by the pharmacist, the oncological injectable preparations should be considered at high microbiological risk as they are intended for use in an immunocompromised patient. However, the microbiological risk class can be lowered from high to medium when the following parameters are simultaneously met:

- Use of the compound within 24 h of preparation
- Preparation through Closed-System Transfer Device (CSTD)
- Use of the compound in the same center in which it was prepared
- Maximum number of preparations per shift per operator (8 preparations/h/shift/operator)

In our oncology pharmacy laboratory, sterile oncological preparations, on the basis of their characteristics, can be made with the automated Apoteca Chemo system in a D-grade environment or with an aseptic manual technique with a double operator in a vertical laminar flow hood of class A placed in a grade C environment. We thus decided to carry out a specific analysis of the microbiological risk of all the oncological preparations made in the institute 2017, comparing our set-up conditions with those required by SIFO.

The aim of this study was to assess the compliance of our institute's Oncology Pharmacy with the microbiological risk standards established by SIFO. This was done by a critical analysis of all the injectable oncological preparations made in 2017 in the center's Oncological Pharmacy.

Materials and Methods

The present study was a retrospective analysis of the preparation of cancer drugs carried out in the Oncology Pharmacy Laboratory of IRST IRCCS in 2017. A multidisciplinary team set up for this task comprised a pharmacist, a member of the Quality Office and an external consultant in charge of methodological support (Studio Emm Effe S.r.l., Milan). The team drew up a list of the oncological preparations produced in the Oncology Pharmacy Laboratory during the year in question and calculated their microbiological risk indexes according to SIFO technical standards. The first phase of the study involved the mapping of the products to be analyzed based on preparation methods, route of administration, final formulation and dosages. The preparations to be assessed were first identified and

Table 1: SIFO technical standards for high microbiological risk preparations.

Preparation area	Background
Preparation in isolator with no operation at microbiological risk outside the isolator	Class D
Preparation in vertical laminar flow hood with low/medium microbiological risk	Class C
Preparation in vertical laminar flow hood with high microbiological risk	Class B

Table 2: Drugs characterization.

Risk	Score	Characterization
High	3	Drugs administered intravenously
Medium	2	Drugs administered subcutaneously
Low	1	Oral Therapy (standards not applicable

a level of contamination risk was attributed to each product using the relative risk indexes (high, value 3; medium, value 2; and low, value 1) based on SIFO technical standards (Table 2). Fulfilment of the following conditions for all types of preparations was checked to evaluate whether the level of risk of product contamination could be reduced:

- Use of the compound within 24 h of preparation
- Preparation *via* CSTD
- Use of the compound in the same center in which it was prepared
- Maximum number of preparations per shift per operator (8 preparations/h/shift/operator)

The re-evaluation of the microbiological risk level also took into consideration specific procedures of our center, including safe transport of preparations in sealed bags, use of vacuum packs, continuous monitoring of transport conditions, and storage temperature of products.

37,830 sterile injections were prepared in 2017 in our oncology pharmacy. 21,474 of these met environmental class requirements as they were prepared through the automated system, certified by the manufacturer as a class A instrument inserted in a class D environment, thus guaranteeing sterility.

Our analysis focused on the remaining 16,356 preparations prepared manually with the double operator technique in class A on background C. Table 3 reports the results of the mapping. The preparations were grouped into categories based on their characteristics and took into account the initial pharmaceutical form, final pharmaceutical form, route and place of administration, and same category grouping of preparations made with different drugs but with similar characteristics. Eighteen categories of products were defined, as shown in the first column of Table 3.

The contamination risk level was identified for each category by attributing a relative risk index (high, value 3; medium, value 2; and low, value 1) based on SIFO technical standards to each product (Table 3, 'Risk ex-ante' column). The presence of conditions that would lower the risk of production contamination was then evaluated and correlated with all set-up conditions, after which the risk of the preparations was revised (Table 3, 'Risk post-ante' column). The evaluation of the aforementioned SIFO conditions revealed that only 9 of the 18 categories of injectable preparations (Table 1), including those of experimental drugs, had risk level 2 because all of the conditions indicated by the standards as medium risk conditions were

Table 3: Results of the mapping.

Tipologie of product						RISK EX ANTE		Conditions that allow reduction of risk				RISK EX POST		FINAL RISK		
DRUG PREPARATION	ROUTE OF ADMINISTRATION AND FINAL FORMULATION			Nome/categoria prodotti oncologici	Number of Drug Preparation 2017	level of contamination risk identified	Value	Use of the preparation within 24 hours of preparation	Set up with closed circuit devices	Use of the preparation in the same facility where the UFA is	Maximum number of preparations per shift (8 prep./h per shift)	level of contamination risk identified used all the conditions	VALUE	ADDITIONAL ACTIONS / BARRIERS ADOPTED	Final level of contamination risk identified	VALUE
Drug Mannually prepared	Intravenous Administration	Final Formulation Bag	VIAL	BRENTUXIMAB VEDOTIN	30	HIGH RISK	3	1	1	0	1	HIGH RISK	3	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
				CARMUSTINE	6	HIGH RISK	3	1	1	0	1	HIGH RISK	3	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
				CLOFARABINE	0	HIGH RISK	3	1	1	0	1	HIGH RISK	3	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
				LIPOSOMIAL DOXORUBICIN	96	HIGH RISK	3	1	1	0	1	HIGH RISK	3	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
				IFOSFAMIDE	173	HIGH RISK	3	1	1	0	1	HIGH RISK	3	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
		Elastomeric Pump	Vial	IFOSFAMIDE	4	HIGH RISK	3	0	1	0	1	HIGH RISK	3	Audit on the patient for microbiological risk. Activation of additional monitoring procedure for high risk products	**HIGH RISK**	**3**
				SODIUM LEVOFOLINATE	9	HIGH RISK	3	0	1	0	1	HIGH RISK	3	Audit on the patient for microbiological risk. Activation of additional monitoring procedure for high risk products	**HIGH RISK**	**3**
		Final Formulation Bag	Vial	FOTEMUSTINE	29	HIGH RISK	3	1	1	0	1	MEDIUM RISK	2	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
				CABAZITAXEL	87	HIGH RISK	3	1	1	0	1	HIGH RISK	3	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
				PACLITAXEL ALBUMIN-BOUND	484	HIGH RISK	3	1	1	0	1	HIGH RISK	3	use of transport in sealed and vacuum-packed bags, controlled and monitored;	MEDIUM RISK	2
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present. This enabled a considerable number of categories of settings to be changed from "high" to "medium" risk. The preparations in question were thus prepared, in accordance with SIFO guidelines, in a room of an environmental class consistent with the risk of their microbiological risk.

Finally, based on the fulfilment of the conditions specified in the SIFO standards, the microbiological risk level was re-evaluated taking into account a number of specific procedures of our center such as safe transport with sealed bags, use of vacuum packs, a continuous monitoring of transport conditions, and storage temperature of products. The results were assessed and improvement actions were identified (Table 3, column 5).

For 9 categories of preparations corresponding to 909 settings, it was possible to change the microbiological risk from high (3) to medium (2), despite the fact that these injectable drugs would be administered in Oncology Units and Services managed by IRST in several local hospitals. However, transport was only authorized after packaging of therapies in heat-sealed bags with a vacuum machine, and after confirmation of maintenance of correct temperature conditions (T<25°C (77°F) and T=2°C to 8°C (36°F to 46°F). When drugs are transported from our oncology pharmacy to operating units outside the hospital, it is standard practice for delivery times and product temperatures to be recorded and verified, in accordance with the institute's Quality Procedure P19 (Procedura di Trasporto Farmaci e Terapie Allestite). Finally, in our study, there were two categories of preparations, equivalent to 13 compounds, for which at least one of the SIFO standards was not met. The microbiological risk for these preparations therefore remained high.

Results

The aim of the present study was to map all the sterile injectable oncological drugs prepared in the Oncology Pharmacy Laboratory of our institute in 2017, calculate their microbiological risk in relation to the type of product (ex-ante risk), assess the degree to which the conditions specified in SIFO technical standards (ex-post risk) were satisfied, map the preparations classed as high-risk by SIFO, and implement improvement actions.

Our analysis shows that only 12 (0.1%) of the 37,830 preparations made in our Pharmacy in 2017 were not in line with SIFO technical standards with regard to the requirements of the on-premises set-up. The preparations in question were those with ifosfamide and sodium levofolinate administered by infusion (4 and 9 preparations, respectively) which were not administered within 24 h of preparation (the therapeutic scheme requires continuous infusion over 24 h). None of these compounds involved an experimental drug. To guarantee the future safety of all preparations, a number of actions will be implemented for specific compounds, e.g., a systematic retrospective audit of patient medical records will be carried out to look for related infections, and systematic sterility checks will be made on each production line for the drugs in question.

Discussion

In conclusion, the lack of literature data bears witnesses to the inadequate evaluation of the microbiological risk of cancer drug preparation. This is an important overlooked problem given that cancer patients often have a compromised immune system. SIFO technical standards indicate that cancer drugs should be prepared in a class A environment in a class B room. However, not all Italian hospitals have the necessary equipment for this and adapting hospital pharmacies would create a major financial burden on the Italian National Health Service. However, it is essential that an assessment of the microbiological risk of preparations be carried out in all situations in which cancer drugs are prepared in conditions other than a class A environment with a class B room [15-19].

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References

1. Crauste-Manciet S, Sessink PJ, Ferrari S, Jomier JY, Brossard D. Environmental contamination with cytotoxic drugs in healthcare using positive air pressure isolators. Ann Occup Hyg. 2005;49(7):619-28.
2. Sessink PJ, Wittenhorst BC, Anzion RB, Bos RP. Exposure of pharmacy technicians to antineoplastic agents: Reevaluation after additional protective measures. Arch Environ Health. 1997;52(3):240-4.
3. Sessink PJ, Timmersmans JL, Anzion RB, Bos RP. Assessment of occupational exposure of pharmaceutical plant workers to 5-fluorouracil. Determination of alpha-fluoro-beta-alanine in urine. J Occup Med. 1994;36(1):79-83.
4. Pethran A, Schierl R, Hauff K, Grimm CH, Boos KS, Nowak D. Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: Monitoring of urinary concentrations. Int Arch Occup Environ Health. 2003;76(1):5-10.
5. Rajan-Sithamparanadarajah R, Roff M, Delgado P, Eriksson K, Fransman W, Gijsbers JHJ, et al. Patterns of dermal exposure to hazardous substances in European union workplaces. Ann Occup Hyg. 2004;48(3):285-97.
6. Mason HJ, Morton J, Garfitt SJ, Iqbal S, Jones K. Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy. Ann Occup Hyg. 2003;47(8):681-5.
7. Sessink PJ, Bos RP. Drugs hazardous to healthcare workers. Evaluation of methods for monitoring occupational exposure to cytostatic drugs. Drug Saf. 1999;20(4):347-59.
8. Sorsa M, Anderson D. Monitoring of occupational exposure to cytostatic anticancer agents. Mutat Res. 1996;355(1-2):253-61.
9. Descoutures JM. Preparation of antineoplastic agents. Ann Pharm Fr. 2006;64(1):7-16.
10. Cazin JL, Gosselin P. Implementing a multiple-isolator unit for centralized preparation of cytotoxic drugs in a cancer center pharmacy. Pharm World Sci. 1999;21(4):177-83.
11. Mason HJ, Blair S, Sams C, Jones K, Garfitt SJ, Cuschieri MJ, et al. Exposure to antineoplastic drugs in two UK hospital pharmacy units. Ann Occup Hyg. 2005;49(7):603-10.
12. ASHP. Guidelines on Handling Hazardous Drugs. Am J Health Syst Pharm. 2006;63(12):1172-91.
13. Good Manufacturing Practices (in French). Agence Franc¸aise de Se´curite´ Sanitaire et des Produits de Sante. 2000.
14. Good Preparations Practices (in French). Agence Franc¸aise de Se´curite´ Sanitaire et des Produits de Sante. 2007.
15. Jahnke M, Kuhn KD. Use of the Hazard Analysis and Critical Control Points (HACCP) risk assessment on a medical device for parenteral application. PDA J Pharm Sci Technol. 2003;57(1):32-42.
16. Panunzio MF, Antoniciello A, Pisano A, Rosa G. Evaluation of HACCP plans of food industries: Case study conducted by the Servizio di Igiene degli Alimenti e della Nutrizione (Food and Nutrition Health Service) of the local health authority of Foggia, Italy. Int J Environ Res Public Health. 2007;4(3):228-32.
17. WHO Expert Committee on specifications for pharmaceutical preparations. World Health Organ Tech Rep Ser. 1996;863:1-194.
18. Hulebak KL, Schlosser W. Hazard Analysis and Critical Control Point (HACCP) history and conceptual overview. Risk Anal. 2002;22(3):547-52.
19. Bonan B, Martelli N, Berhoune M, Maestroni ML, Havard L, Prognon P. The application of hazard analysis and critical control points and risk management in the preparation of anti-cancer drugs. Int J Qual Health Care. 2009;21(1):44-50.