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ORIGINAL RESEARCH

An ISO 31000-Based Risk Matrix for Risk Management in Anticancer Drug Prescription, Compounding, and Administration for Lung Cancer Patients Treated in a Day Hospital Setting

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Background: This study aims to identify and reduce risks that could negatively impact patient safety and organizational aspects related to the different phases of anticancer drug therapy for lung cancer patients in the Day Hospital (DH) care.

Methods: From April 2023 until February 2024, a team of multi-disciplinary healthcare professionals of the National Cancer Institute of Naples, Italy, used a modified Delphi approach to identify the care process, the main activities and related risk factors. The severity of these harms and the probability of their occurrence were assessed by applying a 5×5 semi-quantitative ISO 31000:2018 (ISO 31000) risk matrix. Multiple improvement actions were identified and adopted by the team to reduce the risks to acceptable levels.

Results: Nine main activities, 19 correlated potential risks (10 risks for patient safety domain; 53.0%) (9 risks for organizational area; 47.0%) and 19 mitigation measures were identified. The highest risk levels were recognized in the organizational area for: (i) DH Outpatient Visits, due to delays in patients check-in or lab test results or problems with the prescription software; (ii) anticancer drugs administration, for the unavailability of chemotherapy chairs or lack of dedicated nursing staff. Conversely, risk levels for patient safety area were low overall, because several control measures were already in place. Once the mitigation measures were implemented, a new semi-quantitative risk analysis was performed. Risk levels for organizational area changed from a 44.4% to 0.0% in high level, from 44.4% to 67.0% in moderate level, and from 11.2% to 33.0% in minor level. Risk levels for safety areas did not modify for high level (10.0%), but changed from 50.0% to 10.0% in moderate level and increased from 40.0% to 80.0% in minor level.

Conclusion: ISO 31000 risk management framework applied to lung cancer DH care could improve both organizational and safety objectives in oncology.

Keywords: risk management and assessment, risk matrix, chemotherapy risk, ISO 31000:2018, Day Hospital, lung cancer

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Introduction

The procedures for anticancer drug prescription, compounding and administration in a day hospital setting are high-risk processes due to the multiple interfaces of the different organizational units involved. Generally, the process requires the coordination of numerous activities performed in different hospital units, such as the DH Admissions Unit, the Compounding Antiblastic Drugs Unit of the Pharmacy, and the Chemotherapy Unit. These units participate in the processes of patient admission and anticancer drug prescription, compounding and administration, as well as in the patient discharge process. The risk of errors in all the stages of anticancer drug prescription, compounding, and administration has been described in the literature.[1] These errors could lead to inappropriate treatment, patient injury, or, in some cases, even to patient death.[2,3] Therefore, risk reduction for anticancer drug prescription, compounding, and administration should be a major objective for all Oncology Hospitals.[4] The importance of the problem has been universally recognized and multiple organizations have promulgated recommendations to improve patient safety during chemotherapy treatments.[5] Such recommendations certainly offer an opportunity to improve chemotherapy care and can lead to corrective actions. However, a balanced evaluation of the process must be carried out to identify further possible errors in order to implement strategies for error reduction and mitigation.

Different management methods can assist an organization in improving the quality of care and safeguard healthcare providers, such as the Failure Mode and Effect Analysis (FMEA), the Root Cause Analysis (RCA), the Hazard and Operability Analysis (HAZOP) and Bow-Tie Model.[6] Within the broader context of proactive risk management approaches, ISO 31000 provides guidelines and principles for organizations to identify, assess, and manage risks effectively.[7]

On these bases, we used the risk management framework ISO 31000 to identify and manage the risks related to the different phases of anticancer drug prescription, compounding and administration in the DH setting of our public Cancer Institute in Italy, in order to manage risks that could affect patient safety and negatively impact the organizational aspects of the patient care program, defining the related appropriate mitigation measures and priorities.

Materials and Methods

This risk assessment study aims to highlight possible sources of harm that could negatively affect the whole process of intravenous prescription, compounding and administration of anticancer drug for patients with lung cancer treated within the DH setting. The study was conducted at the National Cancer Institute of Naples, Italy, from April 2023 until February 2024, with the primary objective of improving patient safety and organizational effectiveness of the care program. A modified Delphi approach was used by a team of multi-healthcare professionals to describe and recognize the main processes, sub-processes, risk factors and to identify and prioritize mitigation measures.[8] A 5×5 semi-quantitative ISO 31000 risk matrix was used to assess the severity of the harm and the probability of occurrence, and to define the level of risk. An introductory session aimed to illustrating the purpose of the model and its characteristics to all participants was conducted.

The main processes were identified by an internal group of five professionals from different disciplines (thoracic medical oncology, pharmacist, health management specialist, scientific directorate, and nursing) with the support of a risk management expert. Subsequently, during seven internal meetings, the extended group (eight oncologists, four pharmacists, four nurses, one psychologist, one data manager, and three experts in health and risk management) recognized the main activities performed and identified one or more related risk events. A member (A. Morabito) was the moderator. These experts, at different levels of responsibility, providing care service for lung cancer in the DH setting and visually represented the stages and workflows of patient care.

Risk events were evaluated for their relevance on (i) patient safety and (ii) organizational impact (potential delays in care provision) for patients who underwent intravenous antineoplastic therapies (including chemotherapy, immunotherapy, angiogenesis inhibitors, and monoclonal antibodies). According to the international standard of risk management ISO 31000, a decision matrix risk assessment technique was used to determine and rank risk levels, compare different risks and define which threats needed to be managed first, to identify measures that could minimize the probability and/or consequence of a potential risk. The risk matrix responds to the general principle that the risk level depends on

probability of occurrence of harm (likelihood) and severity of damage (consequences). To overcome the lack of data to develop a quantitative risk matrix and the inherent limitations of qualitative ones, a 5×5 semi-quantitative risk matrix was built to allow the team to further examine either the probability or the harm severity. Both likelihood and impact were scored on a scale of 1–5. Appropriate and differentiated descriptors were used to describe the potential for harm (consequences) for the organizational (Table 1) and patient safety domains (Table 2), while similar descriptors were used to describe the likelihood of an event occurring.

Likelihood has been categorized as (1) rare (once or twice a year); (2) possible (at least once a month); (3) frequent (at least once a week); (4) very frequent (several times a week) and (5) certain to occur (once a chemotherapy session).

The consequences associated with organizational aspects were identified as (1) insignificant (no impact on patient chemotherapy session times); (2) minor (delay of patient chemotherapy session times ≤1 hour); (3) moderate (delay of patient chemotherapy session times >1 ≤3 hours); (4) major (delay of patient chemotherapy session times >3 hours) and (5) very relevant, in the case of postponement of patient chemotherapy session (Table 1). Those related to safety aspects were: (1) insignificant (no treatment required); (2) minor (injury resolved in the chemotherapy outpatient unit or not requiring medical attention); (3) moderate (injury that requires assistance from a medical staff member); (4) major (the harm causes severe or multiple injuries resulting in hospitalization) and (5) very relevant in presence of a permanent disability or patient death (Table 2).

In order to prioritize risks, pre-mitigation risk levels were estimated by the extended group by multiplying likelihood x consequences values and taking into account current measures. The risks were assessed during two dedicated meetings in the presence of all team members to have a mindful and uniform evaluation. The consensus on the likelihood and consequence levels of a potential event was established with an agreement of at least 75.0% among panelists. In the case of lack of consensus, the highest score proposed was considered. No sensitivity checks were performed. The risk score ranged from 1 point (very low) to 25 points (very high). Five color-coded risk levels were used in the semi-quantitative risk matrix to allow a quick assessment of the risk levels: very low (light green, 1–2 points), low (green, 3–4 points), moderate (light orange, 5–12 points), high (dark orange, 15–16 points), and very high (red, 20–25 points). We referred to standard risk color code response

Table 1 Semi-Quantitative Risk Matrix for the Organizational Domain

LIKELIHOOD DESCRIPTORS		**CONSEQUENCE DESCRIPTORS**				
		Insignificant [1]	**Minor [2]**	**Moderate [3]**	**Major [4]**	**Very Relevant [5]**
		No impact on patient chemotherapy session times	**Delay of patient chemotherapy session times ≤1 hour**	**Delay of patient chemotherapy session times >1 ≤3 hours**	**Delay of patient chemotherapy session times >3 hours**	**Postponement of patient chemotherapy session**
Rare [1]	**Once or twice time a year**	1 Very Low	2 Very Low	3 Low	4 Low	5 Moderate
Possible [2]	**At least once a month**	2 Very Low	4 Low	6 Moderate	8 Moderate	10 Moderate
Frequent [3]	**At least once a week**	3 Low	6 Moderate	9 Moderate	12 Moderate	15 High
Very Frequent [4]	**Once a chemotherapy session**	4 Low	8 Moderate	12 Moderate	16 High	20 Very High
Certain to Occur [5]	**Several times a session**	5 Moderate	10 Moderate	15 High	20 Very High	25 Very High
		RISK GRADING COLORS				
		1-2 Very Low Risk	3-4 Low Risk	5-12 Moderate Risk	15-16 HIGH Risk	20-25 Very High Risk

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Table 2 Semi-Quantitative Risk Matrix for the Patient Safety Domain

LIKELIHOOD DESCRIPTORS		CONSEQUENCE DESCRIPTORS				
		Insignificant [1]	**Minor [2]**	**Moderate [3]**	**Major [4]**	**Very Relevant [5]**
		No treatment required	**Injury that can be resolved in the chemotherapy outpatient unit or does not require medical aid**	**Injury that requires aid from Day Hospital medical staff**	**Severe/ multiple injuries resulting in hospitalization**	**Severe/multiple injuries resulting in permanent injury/ disability or patient death**
Rare [1]	Once or twice time a year	1 Very Low	2 Very Low	3 Low	4 Low	5 Moderate
Possible [2]	At least once a month	2 Very Low	4 Low	6 Moderate	8 Moderate	10 Moderate
Frequent [3]	At least once a week	3 Low	6 Moderate	9 Moderate	12 Moderate	15 High
Very Frequent [4]	Once a chemotherapy session	4 Low	8 Moderate	12 Moderate	16 High	20 Very High
Certain to Occur [5]	Several times a session	5 Moderate	10 Moderate	15 High	20 Very High	25 Very High
		RISK GRADING COLORS				
		1-2 Very Low Risk	3-4 Low Risk	5-12 Moderate Risk	15-16 High Risk	20-25 Very High Risk

strategies to establish risk acceptability and tolerability: red described a dangerous level of risk, which was unacceptable and required immediate control; dark orange and light orange identified high and medium levels of risk, respectively; and green and light green colours represented risks considered acceptable.

Multiple risk control measures were discussed and applied by the extended group, when feasible from the organizational and managerial prospective, to reduce the risks to a more acceptable level. After 6 months a new semi-quantitative risk analysis was performed to evaluate the effectiveness of the risk treatment plan and the remaining level of risk following the improvement interventions (residual risk).

The working group recorded data in an Office Word® document and processed it with an Office Excel document®. No individual patient data were collected because the work is a non-interventional study and did not involve patients. It was focused on procedures and healthcare professionals viewpoints.

Results

The study was carried out at the National Cancer Institute of Naples from April 2023 until February 2024 with the purpose to manage risks related to the different phases of anticancer drug therapy for lung cancer patients in DH care. Three sub-process, nine activities and 19 correlated potential risks were recorded for patient safety domain (10 risks; 53.0%) and organizational area (9 risks; 47.0%). The three sub-processes (Figure 1) were identified as: (1) Day Hospital Outpatient Visit (DH-OV); (2) Compounding Antiblastic Drugs (CAD) and (3) Anticancer Drug Administration in Day Hospital (DH-A). For each sub-process, one or more related activities have been identified to describe the workflow of the whole process and facilitate the identification of possible sources of harm. Ten risks (53.0%) were traced to the patient safety domain and nine risks (47.0%) to the organizational area. Seven of the 19 potential risks were related to DH-OV (37.0%), five risks to CAD (26.0%) and seven risks to DH-A (37.0%) sub-processes.

The seven potential risks related to the DH-OV activities were for organizational domain: (1) excessive waiting time in the reception area due to the number of patients booked; delays in drug prescriptions due to (2) delay in obtaining

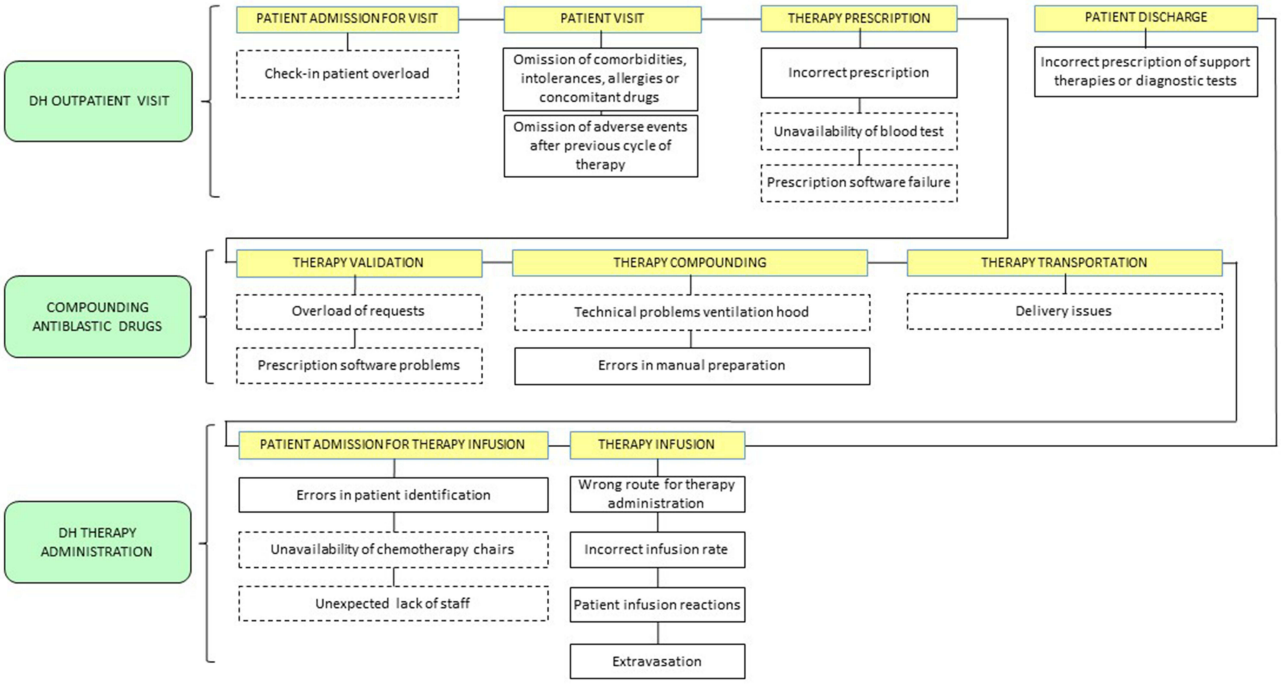

Figure 1 The process of intravenous therapy administration for lung cancer patients in the Day Hospital service divided into three sub-processes (green shapes): (1) Day Hospital Outpatient Visit (DH-OV); (2) Compounding Antiblastic Drugs (CAD) and (3) Anticancer drugs administration in DH (DH-A), with 9 related activities (yellow forms) and 19 potential risks, attributable to the patient safety domain (10 risks, within continuous line shapes) and to the organizational area (9 risks, within dotted line forms).

blood tests or (3) to malfunctioning of the chemotherapy software; for patient safety area: (4) omission of relevant comorbidities, drug intolerances and allergies as well as concomitant meds; (5) omission of adverse events after the previous cycle of chemotherapy; (6) incorrect therapy prescribed by the oncologists or (7) incorrect prescription of supportive therapies or diagnostic tests after chemotherapy session.

Five potential risks were related to CAD and involved, for organizational domain: delay in validation of chemotherapy due to (1) an overload of requests or (2) software problems; (3) delay in the drug preparation due to technical problems of the ventilation hood; for patient safety area: (4) delay in treatment delivery due to logistic problems; (5) errors in manual preparation due to workload and stress.

Seven potential risks were related to DH-A and included for organizational area: excessive waiting time before starting therapy due to (1) unavailability of chemotherapy chairs or (2) lack of adequate nursing staff; for patient safety domain: (3) error in patient identification due to homonymy; (4) incorrect chemotherapy administration route or (5) infusion rate; (6) infusion reactions and (7) extravasation.

The pre-mitigation risk levels, determined by multiplying consequences and likelihood values of the semi-quantitative risk matrix, are reported in the column RL_B in Tables 3 and 4, for organizational and patient safety, respectively.

The risk heat maps in (Figure 2a) show that 44.4% of the risk events recognized for the organizational domain were assigned a high-risk level (4 risks) and a moderate-risk level (4 risks), and 11.2% a low-risk level (1 risk). For patient safety domain, 10.0% of the risk events were assigned a high-risk level (1 risk), 50.0% a moderate-risk level (5 risks), 40.0% a minor-risk level (4 risks). No risk was assessed as very low risk and/or very high risk in both areas (Figure 2b).

Multiple risk control measures were discussed by the working group to reduce exposure to hazards in both domain, 19 in total. In particular, the extended group identified the following six measures for the organizational area (Table 3): (1) three slots scheduled appointments 120 minutes apart to reduce the excessive wait time for check-in at reception and to contain (2) delay in drug prescription due to unavailability of blood tests related to overload issues at the laboratory unit. An emergency paper prescription procedure was implemented to (3) contain the risk associated with the malfunction of the internal chemotherapy prescription software. Two measures have been identified to mitigate the risk (4) of delays in

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Table 3 Risk Factors and Control Measures Related to the Organizational Domain, Before and After Mitigation Actions

RISK ID	SUB-PROCESS	ACTIVITY PERFORMED	RISK DESCRIPTION	L_B	C_B	RL_B	CONTROL MEASURES	CONTROL OWNER	L_A	C_A	RL_A
01.0101	DH Outpatient visit	Patient admission for visit	Excessive waiting time due to entry overload for check-in at reception	3	3	9	Scheduling three slots 120 minutes apart for check-in at reception	Oncologist	2	3	6
01.0201	DH Outpatient visit	Therapy prescription	Delay in drug prescription related to unavailability of blood test for delay in processing at the laboratory unit	5	3	15	Scheduling three slots 120 minutes apart for check-in at reception	Oncologist	4	2	8
01.0202	DH Outpatient visit	Therapy prescription	Delay in drug prescription due to malfunction of the internal chemotherapy prescription software	3	5	15	Emergency paper prescription	Computer Technician	3	4	12
01.0301	Compounding antiblastic drug	Therapy validation	Delay in the therapy validation by the pharmacist due to excessive and concomitant requests	4	3	12	1) Increase the use of "ready to go" procedures 2) Scheduling three slots 120 minutes apart for check-in at reception	Oncologist	3	2	6
01.0302	Compounding antiblastic drug	Therapy validation	Delay in the therapy validation by the pharmacist due to software problems	2	4	8	Emergency paper prescription	Computer Technician	1	4	4
01.0401	Compounding antiblastic drug	Therapy compounding	Delay in drugs compounding due to hood technical problems	1	4	4	Equip the laboratory with an emergency hood	Pharmacist	1	4	4
01.0501	Compounding antiblastic drug	Therapy transportation	Delay in delivery to dh inpatient care/hospital wards due to logistic problems (long walking distances, elevator problems and communication issues)	3	2	6	Increase of dedicated staff	Pharmacist	2	2	4
01.0601	DH Chemotherapy administration	Patient admission for therapy infusion	Excessive patient waiting times due to chemotherapy chairs occupancy in treatment rooms	5	3	15	Scheduling three slots 120 minutes apart for check-in at reception	Oncologist	4	2	8
01.0602	DH Chemotherapy administration	Patient admission for chemotherapy infusion	Long patient waiting times due to understaffing	5	3	15	Modifying the staff's work shifts	Nurse	3	2	6

Abbreviations: L_B, likelihood before risk mitigation; C_B, consequences before risk mitigation; RL_B, risk level before risk mitigation; L_A, likelihood after risk mitigation; C_A, consequences after risk mitigation; RL_A, risk level after risk mitigation.

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Table 4 Risk Factors and Control Measures Related to the Patient Safety Domain, Before and After Mitigation Actions

RISK ID	SUB-PROCESS	ACTIVITY PERFORMED	RISK DESCRIPTION	L_B	C_B	RL_B	CONTROL MEASURES	CONTROL OWNER	L_A	C_A	RL_A
02.0101	DH Outpatient visit	Patient visit	Omission of comorbidities, intolerances, allergies, or concomitant drugs	1	4	4	Implementation and use of a multi-item checklist in the EMR	ONCOLOGIST	1	4	4
02.0102	DH Outpatient visit	Patient visit	Omission of adverse events appeared after previous cycle of therapy	2	3	6	Implementation and use of a multi-item checklist of side effects in the EMR	ONCOLOGIST	1	3	3
02.0201	DH OUTPATIENT VISIT	Chemotherapy prescription	Incorrect chemotherapy prescription	3	2	6	Implementation and use of standardized schedules of chemotherapy prescription and infusion within dedicated software system	ONCOLOGIST	2	2	4
02.0301	Compounding antiblastic drug	Chemotherapy validation	Errors in manual compounding due to workload and stress	1	4	4	1. Double checking by the nursing staff;2. Staff rotation on one-hour shift with a maximum of 8 preparations per hour for each single staff member	PHARMACIST	1	4	4
02.0401	DH Chemotherapy administration	Patient admission for therapy infusion	Errors in patient identification due to homonymy	1	5	5	Identification wristbands for patients	NURSE	1	5	5
02.0501	DH chemotherapy administration	Therapy infusion	Incorrect route for therapy administration	1	3	3	Correct identification of patient and prescription using wristbands	NURSE	1	3	3
02.0502	DH chemotherapy administration	Therapy infusion	Incorrect infusion rate	2	3	6	Use of infusion pumps	NURSE	1	3	3
02.0503	DH chemotherapy administration	Therapy infusion	Infusion reactions	5	3	15	1. A nurse monitors vital signs and side effects (like hypersensitivity, vomiting, extravasation, infiltration, etc) of no more than 4 patients. 2. Presence of a dedicated emergency cart for each room	NURSE	5	3	15
02.0504	DH chemotherapy administration	Therapy infusion	Extravasation	2	4	8	1. Implementation procedure for central venous access: 2. Implementation of a procedure for management of extravasation	NURSE	1	4	4
02.0601	DH outpatient visit	Patient discharge	Incorrect prescription of support therapy or diagnostic tests	2	2	4	Introduction of double discharge planning.	ONCOLOGIST	2	2	4

Abbreviations: L_B, likelihood before risk mitigation; C_B, consequences before risk mitigation; RL_B, risk level before risk mitigation; L_A, likelihood after risk mitigation; C_A, consequences after risk mitigation; RL_A, risk level after risk mitigation.

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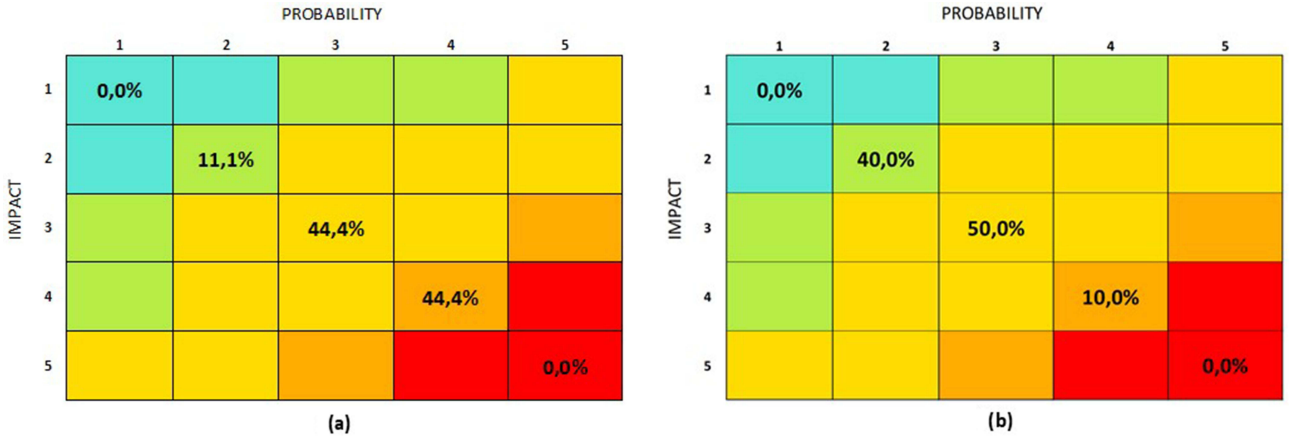

Figure 2 (**a** and **b**) Risk severity heat map before treatment plan. The figures show the risk distribution percentage within the five risk levels before treatment plan. In the organizational area (**a**) the risks are placed in the moderate-high range, while those in the patient safety area (**b**) are placed in the medium-low range.

chemotherapy validation by the pharmacists due to concomitant requests: to increase the use of "ready to go" procedures (that allows starting chemotherapy early in the morning for patients seen the day before); to rely on the positive effects resulting from the planned introduction of the three appointments slots scheduled 120 minutes apart. An emergency procedure for paper prescriptions was also designed to reduce the risk of (5) delay in chemotherapy validation by the pharmacists due to software problems. Furnishing the CAD with an emergency hood minimized the risk of (6) delays in drug compounding due to technical problems. Dedicated staffing has been requested to contain the (7) delay in drug delivery to DH inpatient care due to the hospital layout (long walking distances and elevator problems). The introduction of three appointment slots for check-in at reception has been identified as the best measure to mitigate the risk (8) of excessive patient waiting times due to treatment chair occupancy. Finally, (9) the risk of a long patient waiting time due to an unexpected lack of staffing has been faced with more structured and flexible scheduling of the nursing shifts.

For the patient safety domain the extended group identified the following thirteen measures, as reported in Table 4: (1) the implementation in the Electronic Medical Record (EMR) of a multi-item checklist which includes comorbidities, concomitant medications, intolerances or allergies in order to reduce the probability of physician omissions; (2) the use of a checklist for side effects in the EMR to reduce omissions; (3) the use of a standardized schedule of chemotherapy prescription and infusion within the related information system to avoid incorrect chemotherapy prescriptions; (4) a double check from the CAD staff and (5) a staff rotation of one-hour shifts with a maximum number of eight preparations per hour for each single employee to counter the risk of errors in manual compounding; (6) the use of identification wristbands among patients at the reception area to avoid the probability (already rare) of administration a therapy to the wrong patient due to homonymy; (7) the use of wristbands has been identified as a measure to contain the likelihood of choosing the wrong route for chemotherapy administration, (8) the current use of infusion pumps to avoid incorrect infusion rates. The presence of (9) a nurse to monitor no more than 4 patients at a time, and (10) a dedicated emergency cart for each room was identified as a measure to counteract patient infusion reactions. The implementation of a (11) procedure for the management of extravasation has been recognized to reduce the extravasation risk in addition to (12) the implementation of Port-a-cath or Peripherally Inserted Central Catheter use; lastly (13) a double check of the hospital discharge template has been introduced to control the omission or incorrect prescription of support therapy or diagnostic tests on discharge. Contextually, the individual responsibilities were also outlined for the treatment plan by identifying control owner for both domains.

In February 2024, six months after the implementation of the treatment plan, a new semi-quantitative risk analysis was performed to evaluate the results, determine the current risks, and evaluate the effectiveness of the mitigation

actions. The outputs of this analysis are reported in the last three columns of Tables 3 and 4, while the risk heat maps in (Figure 3a and b) show the percentage distribution of risks among the different levels following the treatment plan.

The risk related to the organizational area has been assigned to only minor risk (3 risks; 33.0%) and moderate level (6 risks; 67.0%). In particular, 4 risks previously classified as high-level (RL_b=15) have moved to the lower moderate risk level ($RL_{a=}$8;12;8;6), while two risks that were already assigned to the moderate risk level (RL_b=8;6) have moved to minor risk-level (RL_a=4). Two risks (RL_b=9;12) improved their risk score, but not their risk level, and continued to be classified as moderate (both RL_a=6), while one risk remained unchanged to low-risk score (RL_a; RL_b=4). The control measures that had the greatest positive impact on the risk level were (i) "Modifying the staff's work shifts" for the risk "Long patient waiting times due to understaffing (ID 01.0602, RL_b=15, RL_A=6, Δ60%)"; (ii) "Scheduling three slots 120 minutes apart for check-in at reception" for the risks "Delay in drug prescription related to unavailability of blood test for delays in processing at the laboratory unit (ID 01.0201, RL_B=15, RL_A=8, Δ46.7%)" and "Excessive patient waiting times due to chemotherapy chairs occupancy in treatment rooms (ID 01.0601, RL_B=15, RL_A=8, Δ46.7%)". For these risks, the risk levels have been classified from high to moderate, with values close to the green area of the risk matrix.

In the area of patient safety, four risks that were previously considered moderate risks ($RL_{b=}$6;6;6;8) have moved to a minor level ($RL_{a=}$3;4;3;4). Taking into account that the area defined as moderate risk already included 4 risks (whose score remained unchanged after the treatment plan), 80.0% (n.8 risks) of the total risks fall in the area of minor risks. The risk score of the remaining two risks remained unchanged and, therefore, they remain, respectively, assigned to moderate (errors in patient identification due to homonymy RL_a; RL_b=5) and high-risk level (infusion reactions RL_a; RL_b=15). The benefits of risk mitigation phase in this area are evident, mainly, for the risks ID 02.0504, ID 02.0102, ID 02.0502. For these risks, the measures, respectively, identified as (i) Implementation procedure for central venous access and Implementation of a procedure for management of extravasation, (ii) Implementation and use of a multi-item checklist of side effects in the EMR, (iii) Use of infusion pumps have lowered the values from moderate to low with a 50% reduction in risk level.

Therefore, for organizational domain four risks classified as high moved to the lower level (moderate) and two risks weighted as moderate moved to the low level, as shown in (Figure 4a). Regarding patient safety, the risk mitigation succeeded in shifting four risks from moderate to low (Figure 4b).

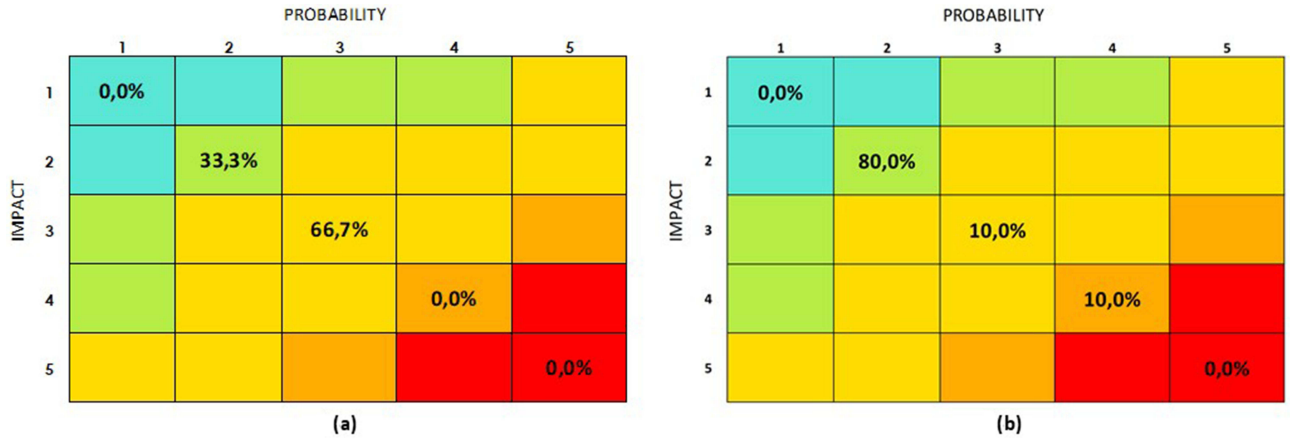

Figure 3 (**a** and **b**) Risk severity heat map after treatment plan. The figures display the risk distribution percentage within the five risk levels after the adopted control measures. These measures had a positive impact especially in the organizational area (**a**), while in the patient safety area (**b**) the measures only impacted those risks which were already classified as moderate.

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PC SCORE 1-25		RISK BT	RISK AT
1 – 2	NEGLIGIBLE	0	0
3 – 4	MINOR	1	3
5 – 12	MODERATE	4	6
15 – 16	HIGH	4	0
20 – 25	CRITICAL	0	0

(a)

PC SCORE 1-25		RISK BT	RISK AT
1 – 2	NEGLIGIBLE	0	0
3 – 4	MINOR	4	8
5 – 12	MODERATE	5	1
15 – 16	HIGH	1	1
20 – 25	CRITICAL	0	0

(b)

Figure 4 (**a** and **b**) Risk transition map. The figures illustrate how the risks level changed after the adoption of risk mitigation strategy for both organizational (**a**) and patient safety (**b**) areas.
Abbreviations: PC, Probability-Consequence; BT, Before Treatment; AT, After Treatment.

Discussion

Three sub-processes, 9 main activities, 19 related potential risk factors and 19 mitigation measures were identified by the multi-professional team involved in the analysis. These risks have been categorized into two major key control areas, namely organizational and patient safety domains. The risks traced to the patient safety area were mainly related to activities carried out during anticancer drug administration in DH and DH Outpatient Visits. Conversely, the number of risks related to the CAD were prevalent in the organizational risk area, followed by outpatient visits in DH and lastly chemotherapy administration. Each risk was weighted using a specific semi-quantitative risk matrix whose scales of consequences and probabilities were defined by the extended group of experts during the meetings. The risks were equally distributed between the two areas, while those with higher scores were mainly concentrated in the organizational domain (delay in drug prescription due to unavailability of lab test results or problems in the prescription software, as well as excessive patient waiting times due to unavailability of chemotherapy chairs or the lack of dedicated staff). Contrariwise, the risk levels in patient safety area were lower, with only one risk worthy of attention, namely the risk of infusion reactions. No risks fell into the red zone or the very high risk level for both domains because the risk magnitude was estimated by taking into account current measures (organizational behaviours and/or use of technological infra-structures) already in place. The two domains have different risk weights likely due to the presence of a clinical risk management services within the hospital. The procedure is probably more focused on managing patient safety rather than organizational issues. This would also explain why the higher risk values characterize the organizational area.

The nineteen measures discussed and then proposed by the extended group have mitigated most risks, by reducing the consequences and/or the probabilities. Eight out of ten risks identified in the patient safety domain are now placed into the green zone of risk matrix, while those related to the organizational area were assigned a minor risk (no. 6) and a moderate level (no. 3).

However, not all risks required reduction and some risks maintained their initial magnitude, because they were already at an acceptably low level. Only the risk associated with infusion reactions has maintained a high score, that cannot be reduced in the probability of occurrence, because it is increasingly frequent with newly approved drugs, such as bispecific antibodies, due to intrinsic drug factors.

At present, one similar experience has been published in terms of risk assessment applied to the whole day-hospital procedures of prescribing, compounding and administration chemotherapy for patients with lung cancer. L. Weber et al applied FMEA to medication errors that may occur during the process of intravenous cancer therapy to guarantee a high standard of patient safety, first, at the University Hospital of Bonn in Germany and, then, at the University Hospital of Cologne; the latter was conducted to evaluate the transferability to another hospital of the catalog of potential failure modes developed.[9] The team identified a total of 52 potential failure modes throughout the whole process of prescribing, compounding, transporting and giving chemotherapy. The most critical errors were associated with the part of prescribing

in both hospitals, including incorrect information about patients (adverse events during the last cycle of chemotherapy were identified as most critical, followed by the failure of having and using incorrect patient parameters like weight) and the use of non-standardized chemotherapy protocols, especially for supportive therapy. They identified appropriate corrective actions for risk reduction, for example, the implementation of a comprehensive electronic prescription software, revising individual chemotherapy protocols to harmonize supportive therapy, and the use of warning messages with the help of pop-up windows in the prescription software (considered useful for dose modifications). Buja et al applied the Failure Mode, Effect, and Criticality Analysis (FMECA) in cancer treatment of outpatient prescription and administration in three organizations in Northern Italy to recognize potential failures and enable the adoption of measures to prevent them.[10] Each criticality was ascertained by rating severity, frequency, and likelihood of a failure being detected, using adapted versions of already published scales. Ten recommendations were proposed for high-risk failure modes with the perspective of limiting these failures or improving their detection. Marzal-Alfaro M et al combined risk analysis using FMECA methodology in antineoplastic production before and after the implementation of an image-based compounding workflow software system, to quantify its impact on reducing medication errors.[1] Overall, 16 potential failure modes were recognized in the pre-implementation phase, while 19 potential failure modes were recognized after software implementation. They identified high-priority recommendations including the identification of the product with the batch and expiration date from scanned bi-dimensional barcodes on drug vials and process improvements in image-based quality control. K. Bourika et al applied the FMECA to chemotherapy preparation in a Central Chemotherapy Preparation Unit of a Public Hospital in Greece to improve the quality and safety of the service.[11] The most important risks identified were the partial compliance of the unit's premises with international standards, the human errors throughout the compounding, labelling, prescribing steps, and the violation of working protocols by employees. Modifying the procedure through the proposed corrective actions enabled a reduction of the Risk Priority Number preparation process from 2102 to 604. J.M. Ouedraogo et al applied the FMEA method to cancer chemotherapy production process at the pharmacy of the National Institute of Oncology in Rabat to evaluate the positive effects of an automated drug dispensing system.[12] They identified 35 failure modes for Phase 1 and 37 for Phase 2. The sum of criticality indexes was 5,957 and 4,586, respectively, for phase 1 and phase 2, corresponding to a criticality reduction of 23.0%.

Risk matrix has become a popular decision-support tool in both the public and private sectors, frequently used also in healthcare organizations, because it standardizes the process of grading the risk.[13] Risk matrix can be applied even where data are limited and does not require specialized expertise. Nevertheless, we are aware of the several limitations of this article, which can be mainly summarized as related to the use of risk matrices in performing a risk analysis, to the concrete implementation of the identified control measures, and to experience of a single group applied to a single process. The first category of limits includes those traditionally associated with the design and use of risk matrices such as the definition of scales (the different levels of likelihood and consequence are very subjective), the possible subjective evaluation errors done by users (better known as representativeness heuristic, availability heuristic and anchoring in addition to adjustment heuristic) and the inevitable subjectivity in the identification and selection of main sources of harm (based on the working experience of team members rather than comprehensive data gathered in the field).[13,14] The second order of limits concerns the application of the measures suggested by the extent group. The team deemed it necessary to identify additional new measures whose effectiveness in terms of risk mitigation still needs to be verified in long-term development. Finally, since it is a single experience related to a patient's treatment pathway for a specific pathology, the analysis reflects the experience of the professionals involved in the study and certainly does not take into account risks observable from an analysis of the data collected in the field, which in any case were not available either before or currently. This, obviously, also limits the capability to translate the same to other Institutions. Nevertheless, we consider our study relevant to the community, as we dedicated a specific risk analysis to develop a safer process related to the different phases of anticancer drug therapy for lung cancer patients in DH care. These findings demonstrate that a structured ISO 31000 aligned risk management framework can significantly reduce organizational risks and enhance patient safety in chemotherapy workflows, providing a practical model for replication in other oncology settings.

Conclusions

The results of this analysis showed that a ISO 31000 risk management framework applied to anticancer drug prescription, compounding and administration by a team of multi-healthcare professionals could improve both organizational and patient safety objectives, by identifying different measures to mitigate the potential risk to acceptable levels.

Abbreviations

DH, Day Hospital; ISO 31000, ISO 31000:2018; FMEA, Failure Mode and Effects Analysis; RCA, Root Cause Analysis; HAZOP, Hazard and Operability Analysis; DH-OV, Day Hospital Outpatient Visit; CAD, Compounding Antiblastic Drugs; DH-A, Anticancer drug administration in Day Hospital; RL_b, Risk Level before risk mitigation; EMR, Electronic Medical Record; RL_a, Risk Level after risk mitigation; PC, Probability-Consequence; BT, Before Treatment; AT, After Treatment; FMECA, Failure Mode, Effect, and Criticality Analysis.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 requires ethics committee approval only for interventional and observational studies involving patients. This was a non-interventional/observational study and did not involve patients. It was focused on procedures and healthcare professionals. No individual patient data were collected. For this reason ethical approval and informed consent from patients were not required.

Consent for Publication

The study participants were fully informed about the nature and purpose of the study and provided their informed consent to be part of this research and to be authors of the manuscript.

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Disclosure

The authors declare no competing interests in this work.

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