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Addition of Infection-Related Patient Assessment to Pharmacist Pre-Preparation Checks Reduces Anticancer Drug Wastage: A Retrospective Analysis

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Abstract

Our group has previously demonstrated that a structured pharmacist review of medical orders against specific oncology treatment criteria, before compounding injectable antineoplastic therapies, effectively minimizes post-preparation medication waste. To optimize these savings and further curtail the loss of prepared oncology agents, we expanded our established checklist to include a clinical assessment of the patient's infection status. This study evaluates how effectively the revised screening protocol reduces waste of compounded injectable anticancer medications. The pre-existing pharmacist checklist used for compounding clearance was supplemented. Beyond the conventional oncology administration criteria, pharmacists evaluated the patient's infection status, defined as a core body temperature ≥ 37.5 °C or an increase in C-reactive protein (CRP) or white blood cell (WBC) levels relative to baseline. We conducted a retrospective analysis comparing the pre-modification and post-modification periods to evaluate changes in the frequency, classification, and financial impact of discarded antineoplastic drugs after preparation, along with the specific clinical reasons for their disposal. Following implementation of the revised screening protocol, the proportion of prepared oncology medications discarded decreased significantly compared with the original framework (0.288% [18/6253] vs. 0.095% [6/6331], P = 0.013). Additionally, the frequency of annual compounding waste specifically attributed to patient infection fell from 11 instances (pyrexia: n = 8; increased CRP or WBC: n = 3) down to a single occurrence (increased CRP: n = 1).Supplementing standard oncology administration benchmarks with a pre-compounding pharmacist review of patient infection status—parameterized by a body temperature ≥ \text{37.5 °C} or elevated baseline CRP or WBC values—serves as an effective strategy to minimize the post-preparation wastage of antineoplastic agents.

Keywords: Anticancer drug, Drug wastage, Cost, Pharmacist, Infection

Introduction

The escalating financial burden of antineoplastic therapies, driven by the emergence of novel therapeutics such as molecularly targeted agents and immune checkpoint inhibitors, poses a mounting global challenge [1, 2]. Implementing interventions to mitigate medication waste stands as a critical cost-containment strategy for oncology pharmaceuticals that preserves the overall quality of patient care [3].

A primary driver of antineoplastic drug wastage involves discarding surplus medication following preparation. Because oncology dosages are tailored to individual patient metrics such as body weight or body surface area (BSA), substantial interpatient dosing variability exists, making the complete exhaustion of single-dose vials difficult [4]. Drug vial optimization (DVO)—which permits the shared utilization of single-use vials across multiple patients—serves as an efficient strategy to minimize leftover oncology pharmaceuticals [5, 6]. Furthermore, rounding prescribed doses to the nearest available vial size, provided the variance falls within an

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established percentage threshold, represents another vital approach used to limit pharmaceutical waste [7-10].

Another source of oncology drug wastage stems from discarding pre-mixed antineoplastic formulations. Most of these therapies are governed by strict eligibility, treatment initiation, dose reduction, and treatment discontinuation parameters. Consequently, dose modifications and therapy suspensions must be guided by the patient's hematological, renal, and hepatic function, as well as the presence of adverse effects. If the decision to modify a dose or halt treatment is made after the required agents have been compounded, the mixed therapies must be discarded. Our group previously demonstrated that a structured protocol enabling pharmacists to review eligibility, initiation, reduction, and discontinuation criteria before compounding injectable oncology therapies successfully minimized post-mixing pharmaceutical waste [11].

Nevertheless, oncological patients exhibit a high susceptibility to infectious complications, as tumor progression and treatment modalities like chemotherapy inherently elevate infection risks [12]. Taha *et al.* [13] observed that pyrexia or infection represents the second most frequent driver of chemotherapy postponement or cancellation, surpassed only by neutropenia. Similarly, a retrospective analysis by Ang *et al.* [14] confirmed that the presence of infectious signs and symptoms, such as fever, is the primary rationale for withholding chemotherapy. Consequently, routine infection monitoring in patients undergoing cytotoxic therapy is imperative. Historically, the thermal threshold for initiating antineoplastic treatment has typically been defined as a body temperature < 38 °C over the preceding 24 hours, and our earlier pharmacist validation framework operated under this benchmark [11]. However, during the execution of that protocol, we encountered scenarios in which patients presenting with a body temperature ≥ 37.5 °C but < 38 °C had their scheduled oncology treatments canceled on the day of administration due to clinical concerns about infection. In these instances, the fully compounded therapies had to be discarded if the cancellation occurred post-preparation. To achieve further reductions in post-mixing oncology drug waste, it may be essential for pharmacists to evaluate a patient's infection-related parameters alongside the core administration criteria established in our prior framework.

The objective of this investigation was to determine the utility of expanding our original pharmacist verification protocol by incorporating an infection-status assessment—parameterized by body temperature ≥ 37.5 °C or elevated baseline C-reactive protein (CRP) or white blood cell (WBC) levels—to mitigate antineoplastic drug waste. Pharmacists evaluated these indicators before drug compounding. We compared the performance of the modified and original protocols in reducing injectable oncology drug wastage.

Materials and Methods

Outline of the problem and modification of the protocol

By applying our previous workflow, in which pharmacists verified eligibility, initiation, reduction, and discontinuation parameters for injectable oncology agents before compounding, we successfully achieved a significant reduction in pharmaceutical waste at our institution [11]. Nonetheless, clinical teams occasionally identified potential infections in patients with body temperatures < 38 °C after the antineoplastic agents had already been mixed, leading to the cancellation of that day's treatment. Consequently, these pre-mixed formulations had to be discarded.

To prevent such unnecessary post-mixing drug disposal, we modified the existing workflow. The revised protocol integrates an evaluation of the patient's infection status based on a body temperature ≥ 37.5 °C or an increase in CRP or WBC levels relative to baseline. Consistent with the previous framework, pharmacists reviewed these parameters before compounding for all inpatients scheduled to receive injectable oncology therapies, excluding agents not compounded by the pharmacy department. If laboratory values violated established guidelines, the pharmacist advised the responsible physician on dose modifications or treatment suspension, per the current protocol. Furthermore, if a patient exhibited a body temperature ≥ 37.5 °C or demonstrated an upward trend in CRP or WBC levels from baseline, the pharmacist recommended that the clinician evaluate the patient for an underlying infectious disease.

Study design and study setting

Operating as a retrospective chart review at a single institution, this investigation was centered at the 614-bed Gifu University Hospital. The study cohort comprised hospitalized individuals undergoing injectable antineoplastic therapy during two distinct blocks: a pre-modification phase spanning April 1, 2019, to March 31, 2020, and a post-modification phase from April 1, 2020,

to March 31, 2021. Patients were excluded from analysis if their prescribed oncological treatments did not require compounding by pharmacy staff.

During the baseline period, pharmacists verified treatment eligibility, initiation criteria, dose reductions, and cessation thresholds before compounding, as described in our previous work [11]. Once the protocol was updated, the pre-compounding checklist was expanded to evaluate whether patients exhibited a body temperature ≥ 37.5 °C or an upward shift in CRP or WBC levels relative to baseline values (**Figure 1**). Excepting cases where medications did not require pharmacy compounding, all inpatients slated for injectable oncological therapies underwent this verification before any drug preparation occurred. If a patient lacked current laboratory workups, the pharmacist prompted the attending clinician to issue the appropriate blood orders. The pharmacist then delivered clinician recommendations for dose adjustments or complete treatment deferral, guided by the patient's real-time lab results and thermal metrics.

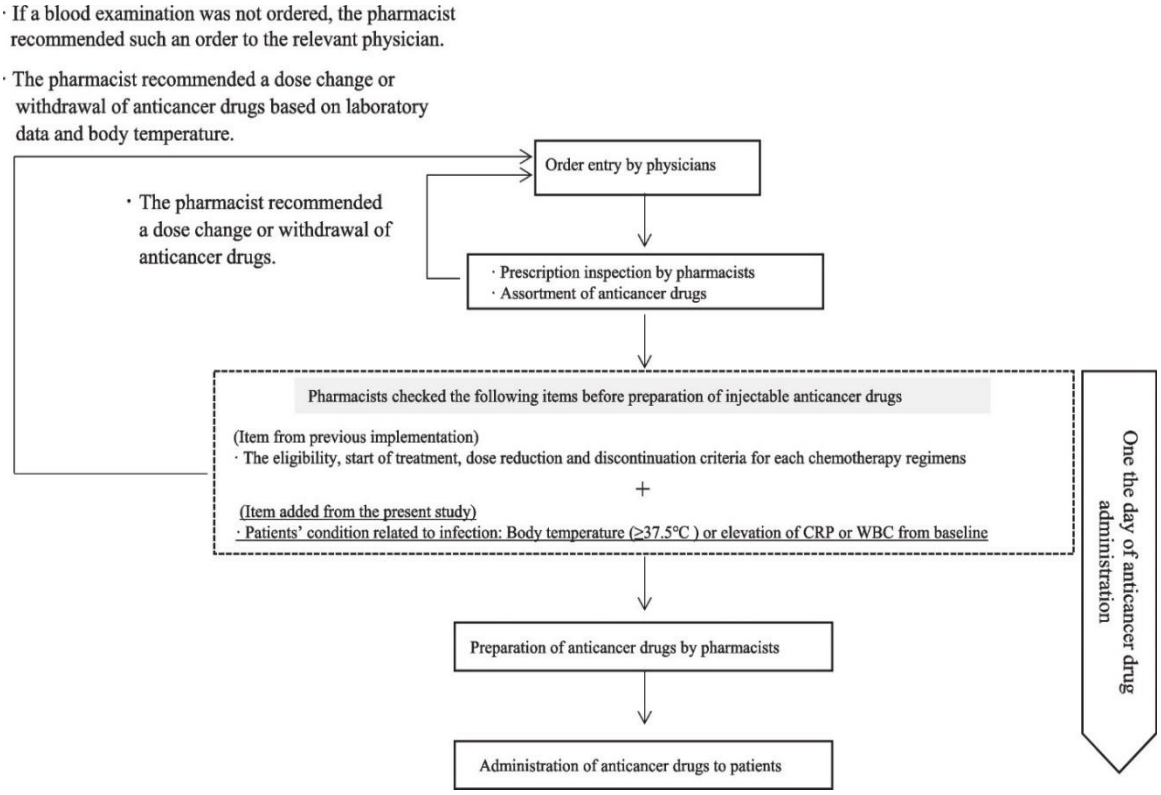


Figure 1. Workflow of the prescription, preparation and administration process performed by the pharmacist in charge of preparing injectable drugs

An institutional database was maintained to capture the volume and pharmacological classes of the antineoplastic drugs, the specific nature of each pre-compounding pharmacist intervention, the frequency of post-preparation disposal, and the precise clinical rationales for discarding the agents. Data from the pre- and post-modification phases were subsequently cross-examined.

Evaluation of the usefulness of the modified protocol

To assess the utility of the protocol revision, we quantified and compared the volumes and financial impacts of antineoplastic agents discarded after compounding across the two study periods. Financial losses from wasted medications were calculated based on the official Japanese pharmaceutical pricing index in effect at the time of drug disposal. For standardized tracking, chemotherapy regimen and chemotherapy cycle were defined according to the National Cancer Institute Dictionary of Cancer Terms: a regimen represents a structured therapeutic program defining specific dosing, scheduling, and duration of antineoplastic therapy, while a cycle refers to a discrete treatment phase paired with a

subsequent recovery period (without treatment) that repeats on a fixed schedule.

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Japan Ltd., Tokyo, Japan). The threshold for statistical significance was set at $P < 0.05$. Variations in the overall volume of administered chemotherapy cycles and the incidence of discarded pre-mixed antineoplastic formulations between the two study periods were evaluated using the chi-squared test.

Ethics statement

This investigation adhered strictly to the human research protocols sanctioned by the ethics committee of the Gifu University Graduate School of Medicine and authorized by the Japanese governing bodies (institutional review board approval no. 2021-A062). Because of the retrospective methodology used in this study, the requirement for obtaining formal informed consent from participants was waived.

Results and Discussion

Patient demographics

Over the entire study window, the patient population accounted for 6253 chemotherapy cycles in the pre-modification era and 6331 cycles following the protocol shift (**Table 1**). A statistically significant difference in the distribution of chemotherapy regimens was observed between the two periods. In the post-modification era, the volume of delivered chemotherapy cycles grew by upwards of 20% for individuals undergoing treatment for gynecologic, colorectal, gastric, breast, and skin malignancies, as well as osteosarcoma and sarcoma; conversely, cycle volume contracted by more than 20% for patients being treated for hepatic, biliary, pancreatic, and brain tumors when compared against the baseline period.

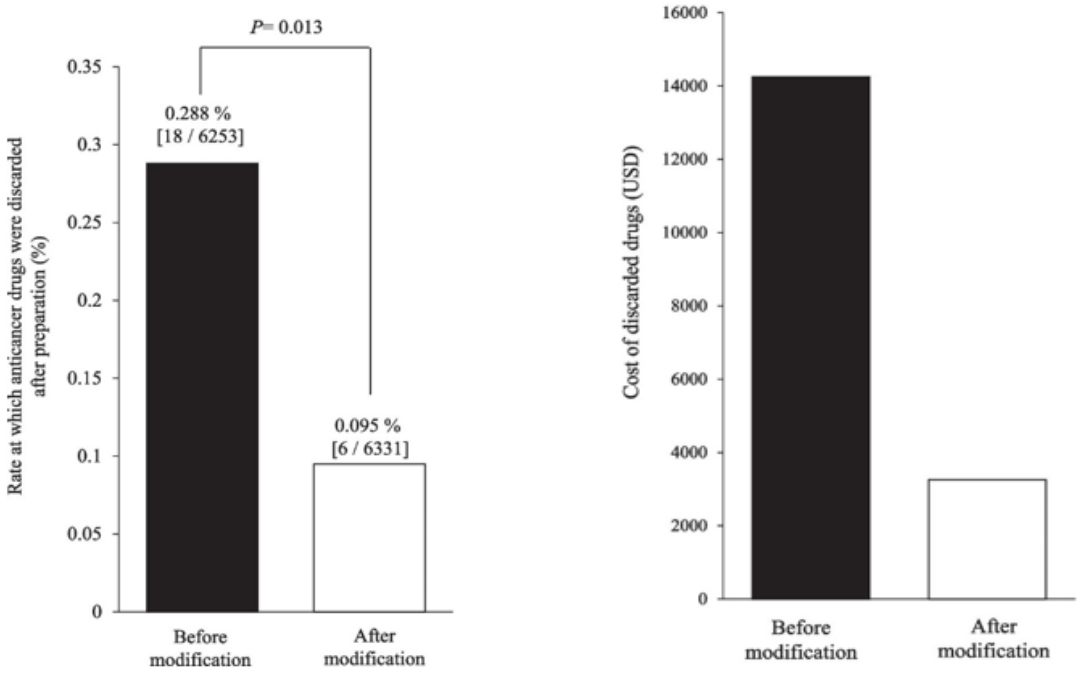
Table 1. Total number of chemotherapy cycles before and after protocol modification

Cancer regimen category	P-value	After protocol modification	Before protocol modification
Hematological malignancies	< 0.001	1268	1400
Lung and respiratory system cancers	—	764	812
Gynecological cancers	—	697	543
Colorectal cancers	—	425	289
Gastric cancer	—	91	66
Esophageal cancer	—	1254	1441
Hepatobiliary and pancreatic cancers	—	153	193
Head and neck/oral cancers	—	399	369
Pediatric cancers	—	535	527
Osteosarcoma and soft tissue sarcomas	—	291	189
Breast cancer	—	13	7
Brain tumors	—	43	69
Urological cancers	—	341	306
Skin cancers	—	31	22
Other malignancies	—	26	20
Total	—	**6331**	**6253**

Data were statistically compared using the chi-squared test

Analysis of waste volumes for intravenous antineoplastic medications

Implementing the revised protocol led to a notable drop in the proportion of prepared antineoplastic therapies thrown away during active treatment cycles compared to the baseline period (0.288% [18/6253] vs. 0.095% [6/6331], $P = 0.013$) (**Figure 2a**). Furthermore, the cumulative economic burden of these discarded, pre-mixed oncology drugs fell sharply from USD 14,247 before the procedural shift to USD 3252 following its adoption (**Figure 2b**).



a) b)

Figure 2. Evaluation of the relative frequency (a) and financial impact (b) of prepared intravenous oncology medications thrown away pre- versus post-procedural revision—statistical significance evaluated via chi-squared analysis.

Under the initial guidelines, the most prevalent catalyst for disposing of prepared chemotherapy agents was patient pyrexia (n = 8, 44.4%), followed sequentially by elevated C-reactive protein or white blood cell counts (n = 3, 16.7%), hematological suppression (n = 2, 11.1%), specific patient requests (n = 2, 11.1%), and isolated deviations in alternative blood laboratory parameters (n = 1, 0.6%) (**Table 2**). After the workflow was updated, drug wastage stemming from elevated CRP, bone marrow suppression, patient preference, and other hematological irregularities each decreased to just a solitary case. Remarkably, pyrexia was ruled out as a driver of medication disposal (**Table 2**).

Table 2. Catalysts driving the disposal of prepared intravenous oncology treatments prior to and following workflow optimization.

Cause for drug disposal	After protocol modification, n (%)	Before protocol modification, n (%)
Infection-related condition – fever (≥37.5 °C)	0	8 (44.4)
Infection-related condition – elevated CRP or WBC	1 (16.6)	3 (16.7)
Patient-requested discontinuation	1 (16.6)	2 (11.1)
Myelosuppression	1 (16.6)	2 (11.1)
Other causes	3 (50.2)	3 (16.7)
Total discarded cases	**6**	**18**

CRP: C-reactive protein, WBC: white blood cell

Clinical details of pharmacist consultations before and following procedural updates

Table 3 details the specific clinical activities performed by pharmacy staff before the reconstitution of intravenous antineoplastic agents across both study phases. The overall volume of clinical actions increased from 141 during the pre-modification phase to 159 during the post-modification phase. Bone marrow suppression was the primary trigger for pharmacy action in both eras (116 [82.2%] initially, compared with 125 [78.6%] after

the change). Meanwhile, the frequency of clinical actions for pyrexia and elevated CRP or white blood cell parameters increased following the workflow revision (fever: 1 [0.7%] vs. 8 [5.0%]; elevated CRP or WBC: 2 [1.4%] vs. 8 [5.0%]).

Table 3. Assessment of clinical actions managed by pharmacy personnel before compounding intravenous chemotherapy treatments across both protocol phases.

Type of intervention (clinical reason)	After modification, n (%)	Before modification, n (%)
Infection-related condition – fever (≥37.5 °C)	8 (5.0)	1 (0.7)
Infection-related condition – elevated CRP or WBC	8 (5.0)	2 (1.4)
Myelosuppression	125 (78.6)	116 (82.3)
Renal impairment	4 (2.5)	10 (7.1)
Hepatic dysfunction	8 (5.0)	9 (6.4)
Electrolyte imbalance	2 (1.3)	3 (2.1)
Anemia	3 (2.0)	0
Peripheral neuropathy	1 (0.6)	0
Total interventions	**159**	**141**

CRP: C-reactive protein, WBC: white blood cell

We demonstrated that integrating a pharmacist-led review of patients' infectious status into an existing protocol—utilizing indicators such as a body temperature ≥ 37.5 °C or baseline elevations in C-reactive protein (CRP) or white blood cell (WBC) count—before compounding anticancer therapeutics led to a major decrease in post-preparation drug waste.

Under our historical protocol, a body temperature threshold of < 38 °C served as the primary administration benchmark before compounding. This standard, however, resulted in 11 annual instances of anticancer medication disposal due to infection-related complications. Over that same timeframe, pharmacists initiated only three infection-related interventions. Following the inclusion of the infection status review to our workflow, annual medication disposals driven by infection fell from 11 cases to a single case. Concurrently, infection-related pharmacist interventions rose to 16 per year. Overall, the total frequency of post-preparation anticancer drug disposal decreased from 18 cases before the protocol update to 6 afterward. This change also translated to a substantial financial impact: the overall cost of discarded compounded oncology drugs plummeted from USD 14,247 before modification to USD 3,252 afterward.

In comparison, Ang *et al.* [14] reported that the aggregate cost of discarded parenteral cytotoxic medications from returned chemotherapy regimens across 72 annual cases at a tertiary care facility totaled 2052 EUR [14]. It is vital to recognize that while the average market price of oncology medications has risen [15], the exact financial savings are inherently tied to the specific types of drugs discarded. From a broader clinical perspective, a retrospective cohort study by Shayne *et al.* [16] established that infection represents a primary risk factor for both in-hospital mortality and extended hospital stays among older oncology patients. Consequently, the protocol detailed here may not only mitigate medical expenditures by decreasing hospitalization duration but also potentially enhance overall patient prognosis.

In this investigation, patient infection assessments were guided by a body temperature ≥ 37.5 °C or baseline increases in CRP or WBC levels. Per the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [17], pyrexia is defined as a core temperature > 38 °C. Furthermore, febrile neutropenia (FN)—a severe, life-threatening complication in chemotherapy patients—is defined by an oral temperature exceeding > 38.3 °C. The European Society for Medical Oncology (ESMO) guidelines define FN as two consecutive readings exceeding > 38.0 °C within a 1-hour window [18]. Accordingly, standard clinical parameters for initiating most anticancer therapies are conventionally set below < 38 °C. Even so, multiple clinical trials define a 'normal' body temperature as < 37.5 °C and utilize a threshold of ≥ 37.5 °C to diagnose underlying infections [19, 20]. In our study, lowering the temperature criterion from < 38.0 to < 37.5 °C increased annual pharmacist interventions from 1 to 8, while concurrently reducing

the number of discarded compounded agents due to suspected infection from 8 to 0.

We also integrated a review of baseline-elevated CRP and WBC counts into the revised workflow. Following this addition, annual pharmacist interventions triggered by elevated CRP or WBC levels rose from 2 to 8, and associated compounding waste fell from 3 cases to 1. Both CRP levels and WBC counts are well-established early biomarkers for infectious processes [21, 22]. Nevertheless, clinicians must note that baseline elevations in these inflammatory markers can also stem from non-infectious inflammatory cascades, particularly those driving cancer development and malignant progression [23-25].

Following the implementation of the modified protocol, six cases of post-preparation anticancer drug disposal still occurred. Among these, three patients met all established administration criteria but had their therapies canceled due to subsequent physician decisions. The remaining three cases involved acute, unpreventable shifts in patient clinical status on the scheduled day of drug administration.

This study has several limitations. First, its retrospective, non-randomized, observational framework introduces the potential for unrecognized patient selection biases that may influence outcomes. Second, we did not quantify the operational burden or human resource demands associated with executing this updated protocol. Finally, this evaluation did not include an explicit analysis of the medical safety outcomes of anticancer drug administration.

Conclusion

This investigation demonstrates that a pre-compounding pharmacist review of a patient's infection status, conducted alongside standard oncology drug administration criteria, serves as an effective strategy for minimizing post-preparation anticancer medication waste.

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Ethics Statement: None

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