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Assessment of the Pharmacoeconomic Impact of Reusing Overfill Prescription Medicines with Closed Dose

Avaliação do Impacto Farmacoeconômico do Reaproveitamento de Overfill de Medicamentos Prescritos com Dose Fechada

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ABSTRACT

Objectives: To evaluate the financial impact and reduction of waste by reusing leftover prescription medication bottles with flat doses in an oncology clinic in the Federal District. **Methods:** Descriptive, retrospective study, from the period between June 2020 and June 2023, on the amount of average *overfill* per vial of pembrolizumab, pertuzumab, atezolizumab and daratumumab SC prescribed in closed doses using closed system devices.The manipulations were carried out under controlled temperature conditions, a clean area environment and validation carried out by 3 pharmacists. **Results:** 121 vials of pembrolizumab (R$ 2,207,675.25) were saved out of 4,656 used, 20 vials of pertuzumab (R$ 267,084.80) out of 564 used, 7 vials of atezolizumab 1200 mg (R$ 150,172.26) in 452 used, 25 bottles of atezolizumab 840 mg (R$ 766,184.75) in 139 bottles used, 12 bottles of daratumumab SC (R$ 328,514.28) in 292 used, totaling R$ 3,719,631.34 in cost reduction in this period, using the cost price as a reference, such as the Brasíndice Factory Price, and closed system security devices. **Conclusion:** The use of a closed system device, combined with clean area validation, pharmaceutical asepsis techniques and good handling practices, allows the use of closed dose medications within 7 days. Considering the volume of manipulations, it is possible to optimize resources and generate savings over accumulated periods. The pharmacist's technical knowledge combined with financial management concepts contributes significantly to the sustainability of institutions.

Keywords: Sustainability. Leftovers. *Overfill.* Reuse.

RESUMO

Objetivos: Avaliar o impacto farmacoeconômico do reaproveitamento de sobras de frascos de medicamentos prescritos com dose fechada em um ambulatório de oncologia do Distrito Federal. **Métodos:** Estudo descritivo, retrospectivo, referente ao período de junho de 2020 a junho de 2023, no qual foi mensurada a quantidade de *overfill* médio por frasco dos medicamentos pembrolizumabe, pertuzumabe, atezolizumabe e daratumumabe SC prescritos em dose fechada e a redução do desperdício com uso destes, utilizando dispositivo de sistema fechado. As manipulações foram realizadas em condições de temperatura controlada, ambiente de área limpa e com a validação realizada por 3 farmacêuticos. **Resultados:** Foram economizados 121 frascos de pembrolizumabe (R$ 2.207.675,25) em 4.656 utilizados, 20 frascos de pertuzumabe (R$ 267.084,80) em 564 utilizados, 7 frascos de atezolizumabe 1200 mg (R$ 150.172,26) em 452 utilizados, 25 frascos de atezolizumabe 840 mg (R$ 766.184,75) em 139 frascos utilizados, 12 frascos de daratumumabe SC (R$ 328.514,28) em 292 utilizados, totalizando R$ 3.719.631,34 de redução de custo nesse período, utilizando como referencial o Preço Fábrica da Brasíndice e dispositivos de segurança de sistema fechado. **Conclusão:** O uso do dispositivo de sistema fechado, combinado com validação da área limpa, técnicas farmacêuticas de assepsia e boas práticas de manipulação, permitem o uso de medicamentos com dose fechada em até 7 dias. Considerando o volume de manipulações, mostra-se possível otimizar recursos e gerar economias no acumulado de períodos. O conhecimento técnico do farmacêutico aliado a conceitos de gestão financeira contribui significativamente na sustentabilidade das instituições.

Palavras-chave: Sustentabilidade. Sobras. *Overfill*. Reaproveitamento.

Introduction

Cancer is considered one of the leading causes of death from Noncommunicable Diseases (NCDs) worldwide. In Brazil, in 2018, it was classified as the second main cause of death from diseases[1]. For the three-year period from 2023 to 2025, 704,000 new cases are expected[2]. It is a multifactorial disease, whose main contributing factors include habits and customs rooted in sociocultural environments, population aging, industrialization, the urbanization process, and lifestyle practices that may involve physical inactivity, obesity, alcohol consumption, and smoking[3,4].

Antineoplastic agents are those that inhibit or prevent the proliferation of cancer cells with malignant characteristics of uncontrolled growth, capable of invading adjacent organs. Based on this, several treatment alternatives are considered, whether aimed at curing the disease, preventing its progression, or providing palliative care[5].

In this context, therapies with monoclonal antibodies have proven to be more effective, with a lower profile of adverse reactions, and with the ability to recognize tumor antigens and selectively induce the immune response, thus avoiding attacks on healthy cells and reducing the overall toxicity profile of the treatment[6,7].

Monoclonal antibodies (mAbs) are immunoglobulins derived from the same clone of B lymphocytes, whose cloning and propagation are performed in continuous cell lines, with the ability to react selectively with specific antigens of each type of cell while preserving healthy ones. Currently, several monoclonal antibody alternatives are available on the market for different types of tumors. Although still a relatively recent treatment option compared to chemically synthesized drugs, they have proven effective in the treatment of malignant solid tumors and hematological diseases[6,7].

However, the cost may compromise the availability of this therapeutic alternative. Monoclonal antibodies account for a high percentage of hospital drug purchase budgets, and for the coming years, projections indicate an unsustainable scenario that could hinder access to treatment. Rationalizing drug costs is an increasingly relevant topic, as all institutions have limited resources for hospital care in the face of human needs[8,9].

When faced with high costs, and in an attempt to reduce resource waste, new alternatives to generate savings must be considered, such as reusing the remaining volume in drug vials. Upon release of a new drug therapy, vials may contain overfill (the injectable product volume that slightly exceeds the amount indicated on the label, ensuring the expected dose for administration, but usually discarded as it is not considered valid leftover)[10]. Some treatment protocols, based on consolidated and evidence-based studies, include monoclonal antibodies prescribed in fixed doses, without variation according to the patient's weight or body surface area. These vials may present residual volumes that, through Good Compounding Practices and the use of Closed System Transfer Devices (CSTDs), can be reused instead of discarded[11,12,13,14].

The amount of leftover volume from these vials depends on the number of patients treated, the scheduling intervals between them, the vial formats available on the market, and the compounding technique applied. Fixed-dose prescriptions of antineoplastic agents allow for forecasting of overfill volumes to generate savings, enabling adjustments in scheduling and patient allocation[15].

Preparation must comply with the current regulations for the compounding of antineoplastic agents in hospital pharmacies, as per ANVISA Resolutions RDC No. 220/2004 and RDC No. 67/2007. The shelf life of these drugs, especially biologics, is not always supported by physical-chemical stability data in their labels for leftover vials, except in cases requiring reconstitution, where instructions usually only refer to maintaining sterility of the formulation[16,17]. With the use of closed system transfer devices, validated cleanroom environments, aseptic pharmaceutical techniques, and Good Compounding Practices, it is possible to ensure the use of these leftovers for up to 7 days[18]. This process tends to reduce the number of vials used throughout treatment cycles, as well as the costs associated with drug use during therapy.

In addition to the direct financial impact, chemical waste from oncology treatments poses high environmental risk and requires specific disposal and final destination measures, generating additional

costs for proper waste management[19]. Thus, it is clear that developing techniques to minimize drug waste is essential, ensuring both safe compounding practices and institutional sustainability.

Objetive

Describe the pharmacoeconomic impact of reusing residual volumes (overfill) from fixed-dose–prescribed antineoplastics using a closed system transfer device in an oncology pharmacy of a private clinic in the Federal District.

Methodology

General Study Characteristics

This descriptive, retrospective study was conducted between June 2020 and June 2023 to analyze the cost-minimization of using closed system transfer devices for reusing residual volumes from fixed--dose–prescribed monoclonal antibodies.

Fixed-dose prescriptions were defined as those in which the entire volume described on the vial label, whether one or more units, was used to prepare a single dose. For example, for a 200 mg dose of pembrolizumab (100 mg/4 mL vial), 8 mL is required for individualized preparation, corresponding to two complete vials.

Residual volume or overfill was defined as any amount exceeding the labeled volume of the vial. Using the same example, a 100 mg/4 mL vial of pembrolizumab, upon aspiration, yields 4.1 mL, meaning 0.1 mL of overfill per vial.

This study reports the opportunity for cost reduction in avoided purchases resulting from preparing monoclonal antibodies with closed system transfer devices, combined with well-defined processes such as the Intelligent Scheduling protocol. This clinical process involves analyzing all patients who use the study medications, their scheduled dates, and doses to ensure they remain within the 7-day stability window that the closed system transfer device guarantees. These factors provide extended stability compared to not using the device, which would otherwise lead to disposal of the vial residues. A cost-minimization analysis was performed based on a decision model (discard or reuse of residues), evaluating the avoided costs from using the closed system transfer device

Standardization of Overfill Volume

To determine the average overfill volume per medication vial, the most common fixed-dose medications routinely handled in the pharmacy were initially selected, totaling six active pharmaceutical ingredients. Three pharmacists independently measured the overfill volume in at least five vials of each medication, obtaining an average overfill per vial. The results were recorded in Microsoft Excel® 2017, as shown in Table 1. The average overfill volumes per vial for pembrolizumab, pertuzumab, atezolizumab, and subcutaneous daratumumab, all prescribed in fixed doses, were 0.1 mL/vial, 0.8 mL/vial, 1.0 mL/vial, and 0.95 mL/vial, respectively. These products were selected for continuation in the project. Subcutaneous rituximab and natalizumab presented average overfills of 0.4 mL/vial and 1.5 mL/vial, respectively, the latter being the highest proportional overfill at 10% of the total vial volume. These two drugs were excluded from the study due to the insufficient number of patients over the monitoring period to enable reuse within the maximum seven-day stability window. After assessing the waste potential, the monitoring of subcutaneous daratumumab was included, as it met all the established criteria.

The handling was carried out under controlled temperature conditions in a cleanroom environment, following Good Compounding Practices in a Class II B2 Biological Safety Cabinet. The volume of patients under treatment and the maximum interval between administrations were recorded, observing the limit of 7 days (the period during which the closed system device ensures sterility of the opened vial in a controlled environment).

For each prescription of these items, a closed system device was attached to the vial, and the amount of residual overfill was recorded in an Excel® 2017 spreadsheet, enabling pharmacists to monitor the expiration date daily for reuse in new prescriptions. Pharmaceutical interventions with the medical team for scheduling adjustments according to patient volume (Smart Scheduling) proved essential to maximize opportunities for extending the validity of overfills and avoiding potential waste.

Table 1: Average Overfill per Vial in Antineoplastic Agents Used in an Oncology Pharmacy of a Private Clinic in the Federal District. 2020–2023Source: Author's own elaboration

	Average Overfill	Total Vial Volume	% Overfill over total volume	Volume x Stability
Natalizumab	1.5 mL/Vial	15.00	10%	NO*
Atezolizumab 840 mg	1.0 mL/Vial	14.00	7%	YES
Daratumumab SC	0.95 mL/Vial	15.00	6%	YES
Pertuzumab	0.8 mL/Vial	14.00	6%	YES*
Atezolizumab 1200 mg	1.0 mL/Vial	20.00	5%	YES
Rituximab SC	0.4 mL/Vial	11.70	3%	NO*
Pembrolizumab	0.1 mL/Vial	4.00	3%	YES

Cost-Minimization Analysis

Cost-minimization studies are conducted when there is a need to compare two or more programs that are equivalent in effectiveness, and the comparison is based exclusively on cost[20]. A cost-minimization analysis was carried out using a decision model (discarding or reusing leftovers), evaluating the costs avoided through the use of a closed system transfer device (CSTD).

To assign value to each vial, the Brasíndice price list for the Federal District (Electronic Brasíndice, version 8.5, Edition 1015, updated on 02/17/2023, with a 17% tax rate applied for the Federal District) was used. The Brasíndice value was multiplied by the number of vials whose purchase was avoided, since after continuous reuse of leftovers, a full vial was returned to stock, making a new purchase unnecessary.

Results

The comparison was carried out as shown in Table 2, which analyzes the period with the established cost-reduction process, and Table 3, which analyzes the period without the established cost-reduction process. It is possible to observe the number of vials used for each drug (i.e., patient consumption), multiplied by the unit Brasíndice price, resulting in the total cost for the analyzed period. In Table 2, the "Purchases Avoided" column shows the vials reused within the continuous process, also multiplied by the Brasíndice value, producing the "Cost Avoided" column, which demonstrates the value of purchases avoided due to the implemented process. Therefore, the Total Cost value for both tables is the same in the two scenarios since all doses were administered, while the "Purchases Avoided" and "Cost Avoided" are present only in the table with the implemented process, indicating a reduction of BRL 3,719,631.34 in drug purchases.

With the implementation of the leftover reuse process between June 2020 and June 2023, 121 vials of pembrolizumab (R$ 2,207,675.25) were saved out of 4,656 used, 20 vials of pertuzumab (R$ 267,084.80) out of 564 used, 7 vials of atezolizumab 1200 mg (R$ 150,172.26) out of 452 used, 25 vials of atezolizumab 840 mg (R$ 766,184.75) out of 139 used, and 12 vials of subcutaneous daratumumab (R$ 328,514.28) out of 292 used, totaling R$ 3,719,631.34 in cost reduction during this period. The Factory Price from Brasíndice was used as the cost reference, with the application of closed-system transfer devices, as shown in Table 4.

Discussion

The pharmacist plays an essential role in the medication supply chain, which generates costs at every stage, from the planning and procurement of medications to the disposal of residual chemical waste (Figure 1). This professional is responsible for optimizing institutional resources, constantly seeking alternatives to minimize waste and implementing sustainable management in drug purchasing. Figure 1: Medication supply chain in an Oncology Pharmacy

Table 2: Cost of the Overfill Utilization Process in Antineoplastic Treatment at an Oncology Pharmacy of a Private Clinic in the Federal District, 2020–2023

Medication	Patient Consumption	Purchases Avoided	P.F. (DF 17%) (R$)	Total Cost wit Consumed Medications (R$)	Avoided Expenditure (R$)	Consumption/ Savings
Daratumumab SC	292	12	27,376.19	7,993,847.48	328,514.28	24,33
Pembrolizumab	4,656	121	18,245.25	84,949,884.00	2,207,675.25	38,48
Pertuzumab	564	20	13,354.24	7,531,791.36	150,184.75	28,20
Atezolizumab 1200	452	7	21,453.18	9,696,837.36	150,172.26	64,57
Atezolizumab= 840	139	25	30,647.39	4,259,987.21	766,194.75	5,56
				114,432,347.41	3,719,631.34	

Source: Author's own elaboration

Table 3: Cost of the standard process for antineoplastic treatment at an oncology pharmacy of a private clinic in the Federal District, 2020–2023.

Medication	Patient Consumption	Purchases Avoided	P.F. (DF 17%) (R$)	Total Cost wit Consumed Medications (R$)	Avoided Expenditure (R$)	Consumption/ Savings
Daratumumab SC	292	0	27,376.19	7,993,847.48	–	0
Pembrolizumab	4,656	0	18,245.25	84,949,884.00	–	0
Pertuzumab	564	0	13,354.24	7,531,791.36	–	0
Atezolizumab 1200	452	0	21,453.18	9,696,837.36	–	0
Atezolizumab= 840	139	0	30,647.39	4,259,987.21	–	0
				114,432,347.41	–	

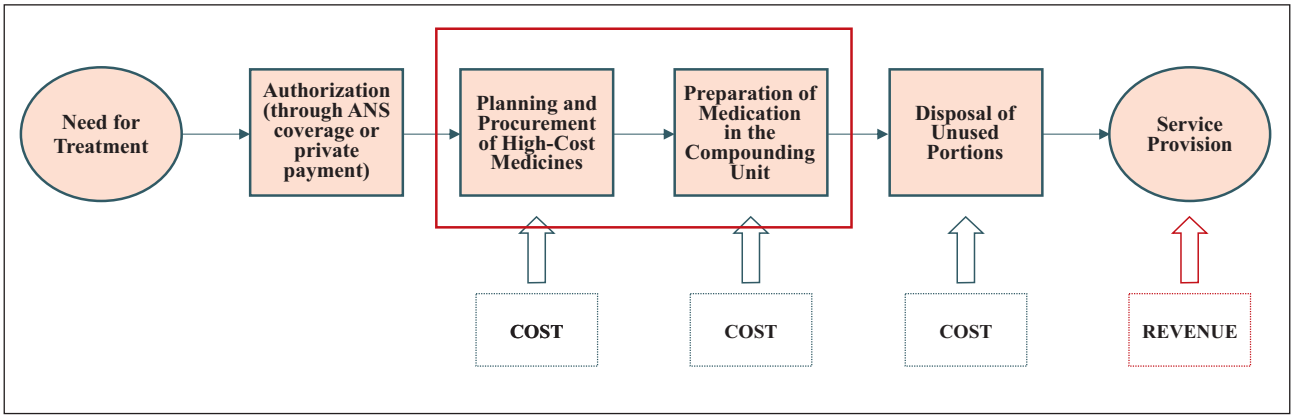
Source: Author's own elaboration

Table 4. Comparative Table of Avoided Purchases

	Comparative Medication Table			
	Pembrolizumab	Atezolizumab*	Daratumumab SC	Pertuzumab
Vials consumed	4,656.00	591.00	292.00	564.00
Avoided Purchase Vials	121.00	32.00	12.00	20.00
Consumption/Cost Reduction Ratio	38.44	18.47	24.33	28.20
Avoided Purchase Overfill	0.10	1.00	0.95	0.80
Value of Avoided Purchase	2,207,675.25	916,357.01	328,514.28	267,084.80
Device Cost (per Dose)	69,842.10	17,730.00	8,760.00	16,920.00
Cost per Reused Vial	0.07	0.03	0.03	0.03

Source: Author's own elaboration

Figure 1. Medication supply chain in an Oncology Pharmacy



Source: Author's own elaboration

Medication vials have a pre-defined stability established by the pharmaceutical industry, considering physicochemical and microbiological aspects. According to RDC/ANVISA 67/2007, which regulates the standards for the preparation of antineoplastic drugs, the shelf life must be based on physicochemical stability data, provided sterility is guaranteed. It is necessary to verify whether the product has been diluted or will be reconstituted, in addition to determining whether the analysis refers only to the leftover portion in the vial or to the diluted product prepared for administration, since these represent entirely different stabilities. Pembrolizumab, pertuzumab, atezolizumab, and daratumumab (SC) have a short stability guaranteed by the manufacturer in the package insert after vial opening, making the handler responsible for discarding the vial after this period due to possible loss of sterility, since the integrity of the vial has been compromised.

An alternative to prevent such disposal involves the use of closed system transfer devices (CSTDs). These devices, designed to ensure extended stability, are mechanically sealed. As such, they are capable of retaining drug aerosols to which they are connected, and are considered closed transfer systems from a microbiological standpoint. Manufacturers guarantee sterility of vials for up to seven days when aseptic techniques are followed and appropriate storage conditions are maintained[17]. It is important to note that, in practice, vial stability is often renewed before the maximum seven-day period, since the demand for these medications is frequent, which makes reuse feasible.

A similar reuse study was conducted by AP Azambuja et al. between January 2018 and June 2021 with the drug eculizumab, used in the treatment of patients with Paroxysmal Nocturnal Hemoglobinuria. Over the 42-month period, 10 patients consumed a total of 1,497 vials, generating a total cost (without considering leftovers) of R$ 19,442,505.00. During this period, 50 vials of eculizumab overfill were recovered, resulting in a cost saving of R$ 649,382.29. This outcome also contributed to ensuring patient access to treatment, including in the case of one patient who developed Budd–Chiari Syndrome after acute thrombosis, with high risk of liver failure and death. This patient used the overfill vials, with improvement of the thrombotic condition and reduced risk of death during hospitalization, and continued to benefit from the leftover vials for another eight months until treatment was judicially authorized[12].

Based on the results obtained, it is possible to conclude that the reuse of leftover drugs prescribed in fixed doses is advantageous for the pharmacoeconomic sustainability of healthcare institutions. As limitations of the study, issues such as patient non-adherence to the correct treatment interval according to protocol and unexpected changes in patient scheduling must be considered, requiring active coordination with the medical and nursing teams.

Conclusion

The high cost associated with the use of monoclonal antibodies can pose significant challenges for the financial management of healthcare institutions. The pharmacist's technical expertise, combined with financial management principles and patient care process strategies, not only enables substantial cost reductions but also alleviates financial burdens, supporting the sustainability pillar of any institution. Despite being a meticulous and structured practice, the reuse of remainders through closed-system transfer devices has proven to be a financially advantageous alternative, ensuring economic sustainability and presenting itself as a potential standardized process to reduce waste in healthcare settings.

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