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Pharmacovigilance Program impact on notifications of adverse reactions to antineoplastic drug in a university hospital

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Abstract

Objective: To evaluate the Pharmacovigilance Program impact on notifications of adverse reactions to antineoplastic drugs (ADR) in a university hospital. **Methods:** Cross-sectional, descriptive and retrospective study, carried out by surveying spontaneous notifications of suspected antineoplastic ADR arising from hospitalization and chemotherapy outpatient clinics and sent to the Pharmacovigilance Program of the Clinical Pharmacy section, of the Pharmacy Service of a university hospital in Porto Alegre. This work was approved by the Research Ethics Committee of that institution under number 2019-0408. **Results:** In 2020, the Pharmacovigilance Program received 71 notifications involving antineoplastic ADR, representing 59.7% of the total notifications received. In 2021, ADR notifications involving antineoplastics represented 47% (n=49) of notifications received. In 2022, the notifications received had an even greater reduction, with 24, representing 37% of the total notifications received in the year. In the year 2023, however, it was possible to observe an increase both in the number of spontaneous reports suspected of total ADR (n=95), as well as in the number of antineoplastics (n=45) and, consequently, in the percentage of spontaneous reports suspected of ADRs. antineoplastic ADR (47%). **Conclusion:** The notifications monitoring involving antineoplastics by Pharmacovigilance demonstrated the need to formulate a strategy to return to the notifier with educational objectives in conjunction with professionals from the chemotherapy outpatient clinic and the care area involved in the notifications.

Key words: pharmacovigilance, antineoplastics, adverse drug reactions.

Impacto da atuação do Programa de Farmacovigilância nas notificações de reações adversas a medicamentos antineoplásicos em um hospital universitário

Resumo

Objetivo: Avaliar o impacto da atuação do Programa de Farmacovigilância nas notificações de reações adversas a medicamentos (RAM) antineoplásicos de um hospital universitário. **Métodos:** Estudo transversal, descritivo e retrospectivo, realizado através do levantamento das notificações espontâneas de suspeitas de RAM antineoplásicos oriundas da internação e do ambulatório de quimioterapia e encaminhadas ao Programa de Farmacovigilância da seção de Farmácia Clínica, do Serviço de Farmácia de um hospital universitário de Porto Alegre. Este trabalho foi aprovado pelo Comitê de Ética em Pesquisa da referida instituição sob o número 2019-0408. **Resultados:** Em 2020, o Programa de Farmacovigilância recebeu 71 notificações envolvendo RAM antineoplásicos, representando 59,7% sobre o total de notificações recebidas. Em 2021, as notificações de RAM envolvendo antineoplásicos representaram 47% (n=49) das notificações recebidas. Em 2022, as notificações recebidas tiveram uma redução ainda maior, com 24, representando 37% do total de notificações recebidas no ano. Já no ano de 2023, entretanto, foi possível observar um aumento tanto no número de notificações espontâneas suspeitas de RAM totais (n=95), assim como na de antineoplásicos (n=45) e, consequente, na percentagem de notificações espontâneas suspeitas de RAM antineoplásicos (47%). **Conclusão:** O monitoramento das notificações envolvendo antineoplásicos pela Farmacovigilância demonstrou a necessidade de formular uma estratégia de retorno ao notificador com objetivo educativo em conjunto com os profissionais do ambulatório de quimioterapia e a área assistencial envolvida nas notificações.

Palavras-chave: farmacovigilância, antineoplásicos, reações adversas a medicamentos.

Introdução

Pharmacovigilance is defined by the World Health Organization (WHO) as the science and activities related to the identification, assessment, understanding, and prevention of adverse effects or any other drug-related problems[1]. It represents an essential component of public health programs, contributing to the evaluation and monitoring of drug safety in clinical practice[2]. Alongside drug safety management services, pharmacovigilance is an indispensable requirement for the early detection of drug-associated risks and the prevention of adverse drug reactions (ADR)[2].

ADR are defined as "any harmful or undesired response to a drug that is unintended and occurs at doses normally used in humans for prophylaxis, diagnosis, therapy of disease, or for modifying physiological functions[3]." They can be classified according to the mechanism by which they are produced, the frequency of occurrence, severity, expectation, and degree of causality[4]. Traditionally, ADR are classified into two major groups: Type A (predictable reactions) and Type B (unpredictable reactions), according to Rawlins and Thompson's definition[4].

Potentially hazardous drugs are those that carry an increased risk of causing significant harm to patients due to failures in the utilization process[5]. Thus, antineoplastic agents are of particular importance because they have a narrow therapeutic index, high potential to cause adverse events, and their therapeutic response and toxicity are related to the plasma concentration of the drug and its duration in the body. Therefore, they are considered potentially hazardous drugs, requiring high vigilance in all stages of their use[5]. The narrow therapeutic index of antineoplastic agents necessitates an evaluation of the adverse reactions resulting from this type of treatment, with pharmacovigilance being responsible for recognizing immediate infusion-related adverse reactions, as well as their severity and alternatives for control and prevention[3].

Different methods can be employed in pharmacovigilance for the identification of ADR, including passive or active surveillance methods. Spontaneous or voluntary reporting is the most widespread and cost-effective passive surveillance method, driven by the motivation of individuals to report the occurrence of an adverse event to a local or national pharmacovigilance center[1]. It can provide information on the relative risk to groups, factors, and clinical issues related to the knowledge of serious adverse reactions, being considered a non-interventional hypothesis-generating and low-cost method. Additionally, it is the preferred method for initiating a pharmacovigilance system, whether local, regional, national, or international[1].

In this context, several pharmacovigilance studies applied to the field of oncology have been published in the literature, demonstrating the importance of the topic[6-16]. In Brazil, most of these studies have been conducted by oncology centers[8,10,11], university hospitals[6,7,12], oncology hospitals[9,11], whether classified as Sentinel Hospitals[6,12] or not, showing that the prevalence of adverse reactions as a cause of hospitalization in oncology patients is extremely variable and still unclear[17]. According to data from the European Union, ADR are responsible for almost 5% of hospital admissions, with 197,000 deaths annually attributed to them in 2005. Additionally, studies indicate that 100% of patients undergoing antineoplastic chemotherapy experience at least one ADR, with an average of two to seven ADR per cancer patient being considered normal[18].

Thus, the importance of the Pharmacovigilance Program's role was recently highlighted with the publication of the profile of ADR notifications for antineoplastic drugs submitted to the said program from a university hospital in Porto Alegre, enhancing medication safety in the hospital[6] environment. In this context, continuing the previously initiated work, the present study aimed to evaluate the impact of the Pharmacovigilance Program's activities on ADR notifications for antineoplastic drugs at a university hospital.

Métodos

This is a cross-sectional, descriptive, and retrospective study conducted through the survey of spontaneous reports of suspected ADR to antineoplastic drugs from hospital admissions and the chemotherapy outpatient clinic, submitted to the Pharmacovigilance Program of a university hospital in Porto Alegre.

This healthcare institution is considered highly complex and is certified by the Joint Commission International (JCI) Accreditation. It has approximately 850 inpatient beds and an average of 470,000 outpatient visits per year.

The Pharmacovigilance Program is part of the Drug Information Center (CIM) and belongs to the Clinical Pharmacy section of the Pharmacy Service at the university hospital in Porto Alegre since 2001, in line with the creation of the Sentinel Network by ANVISA. Its activities are carried out by four contracted clinical pharmacists, working 40 hours a week, and one pharmacy student, working 20 hours a week, who perform all CIM activities, including those related to pharmacovigilance. The professionals and students are trained for a minimum of 20 hours based on the adverse reaction investigation flowchart shown in Figure 1.

Voluntary and anonymous reports of suspected ADR can be submitted electronically by filling out a specific form by healthcare professionals, containing the minimum required information: date and time of the event, presence or absence of harm, medical record number, full name, date of birth, age, sex, department where the event occurred, suspected drug, signs and symptoms, and the patient's clinical history.

The system is called Operational Strategic Management (GEO) through the Interact Suit SA 8 software (Strategic Adviser - SA, Occurrence manager - OM module), available on the hospital's intranet (Figure 2). In this same system, the notifier can be identified. It is worth mentioning that other forms of reporting are also accepted by the institution, such as email, phone call, or verbal report. Additionally, the hospital's Ombudsman can forward received situations. Furthermore, the Pharmacovigilance Program is disseminated throughout the hospital through the biannual CIM Bulletin, which dedicates a section to active pharmacovigilance information.

These reports of suspected ADR are received by the Risk Management team, which, together with the Pharmacovigilance Program, manages and analyzes the reports based on causality relationship (according to the Naranjo algorithm[19]), predictability (according to Rawlins and Thompson[4]), and severity (according to ANVISA classification[1]). All confirmed serious ADR with defined causality are recorded in ANVISA's VIGIMED system. The investigation and analysis of suspected ADR follow the flowchart established by the Clinical Pharmacy section of the hospital (Figure 1).

Figure 1. Flowchart of adverse drug reaction investigation from the Pharmacovigilance Program of the Clinical Pharmacy Section at the Pharmacy Service of the university hospital in Porto Alegre.

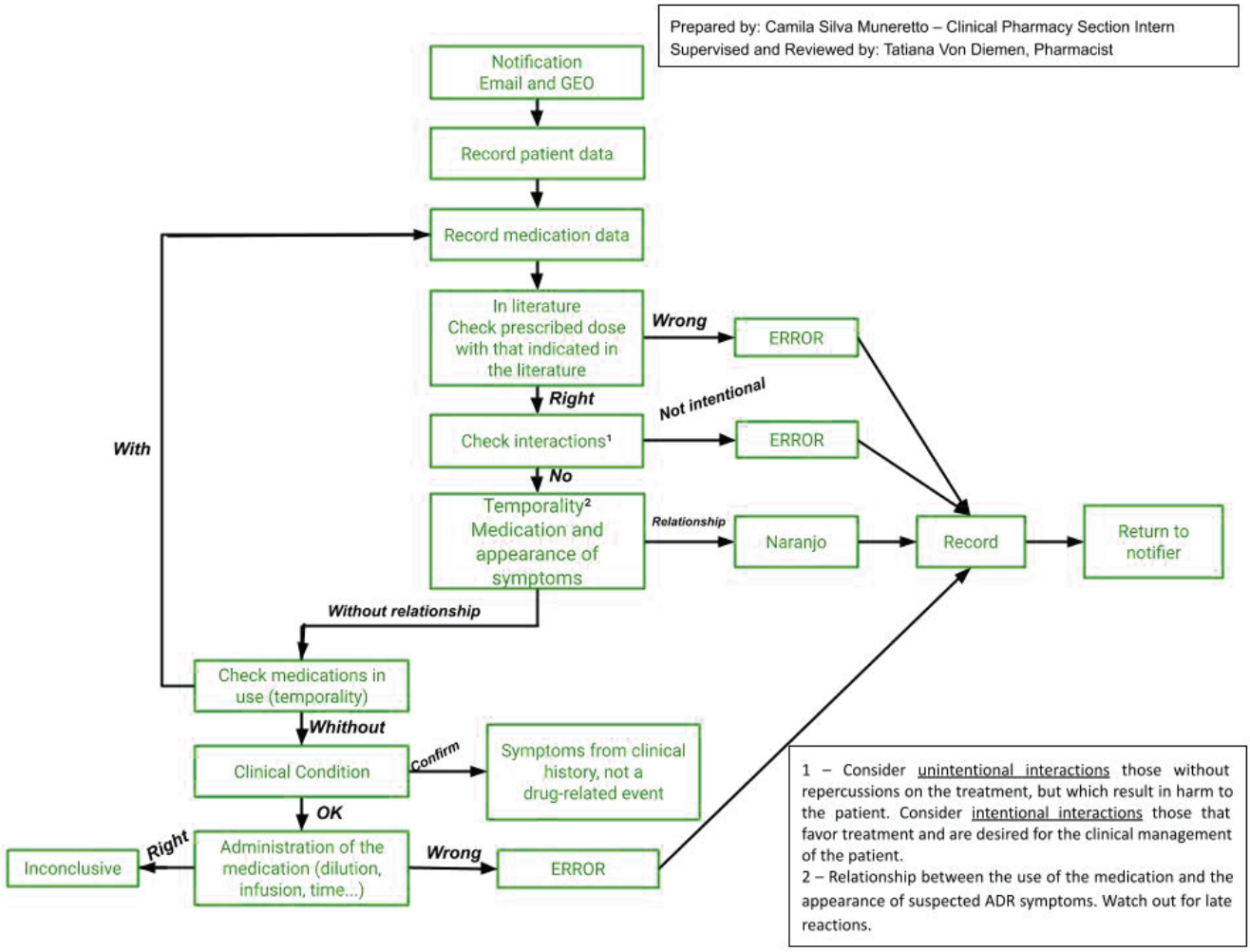
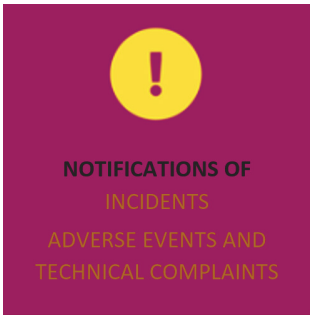


Figure 2. Incident Notification, Adverse Events, and Technical Complaints Identifier used by the institution through its intranet.



Given the high percentage of spontaneous reports of suspected ADR related to antineoplastic drugs sent to the program in 2020, the Pharmacovigilance Program proactively planned an improvement in its workflow, considering two stages: 1) starting January 1, 2021, a feedback system to the notifier was implemented for 100% of the reports received. This procedure consists of a form in Word® format with the title of the notification plus patient data, notifier's identification and profession, the origin of the notification (verbal or electronic), the suspected drug, event description, underlying disease, suspected reaction, notification evaluation, outcome, actions taken after pharmacovigilance analysis, as well as causality relationship according to the Naranjo algorithm[19,20], predictability according to Rawlins and Thompson[4], and severity according to ANVISA[1]; 2) incorporating in the feedback document to the notifier a suggestion of pre-medication for the next chemotherapy cycle, according to the patient's current chemotherapy protocol, in line with the recommendation of the drug's monograph as per the Lexicomp® Wolters Kluwer database.

It is noteworthy that the feedback on the analysis of suspected ADR reports is given to the notifier within a maximum period of 30 days, with those classified as severe prioritized for the earliest possible response.

Data from all reports received from 2020 to 2023 were collected using the database of the said Pharmacovigilance Program with Microsoft Office Excel® 2016. This study was approved by the Ethics Committee of the institution under the number 2019-0408.

Resultados

The total number of antineoplastic drug prescriptions at the university hospital in Porto Alegre from 2020 to 2023, both in the chemotherapy outpatient clinic and inpatient, is shown in Table 1. As demonstrated, an average of 18,000 prescriptions were made each year, with the majority originating from the chemotherapy outpatient clinic, representing approximately 65% of the total antineoplastic chemotherapy prescriptions in the period analyzed.

Table 1. Number of Antineoplastic Drug Prescriptions in the Chemotherapy Outpatient Clinic and Inpatient Unit of a University Hospital in Porto Alegre from 2020 to 2023.

Nº of Antineoplastic Drug Prescriptions (%)	2020	2021	2022	2023
Chemotherapy Outpatient Clinic	11042 (65.0)	10117 (62.1)	11633 (63.6)	13121 (67.5)
Inpatient Unit	5938 (35.0)	6165 (37.9)	6667 (36.4)	6329 (32.5)
Total	16980 (100)	16282 (100)	18300 (100)	19450 (100)

According to institutional information, the total number of outpatient visits increased by 23% between 2020 and 2021. From 2021 to 2022, the increase was 15%. Between 2022 and 2023, there was a 4.5% increase in outpatient visits.

The Pharmacovigilance Program of the university hospital in Porto Alegre received an annual average of 97 spontaneous reports involving all suspected ADR during the study period. Of these, approximately 48% were related to antineoplastic therapy, as shown in Figure 3. Other reports not involving antineoplastic therapy were mainly related to antimicrobials, opioid analgesics, contrast agents, anticonvulsants, among other pharmacological categories.

In 2020, the data collection form used by the Pharmacovigilance Program was not structured to include demographic data. Starting in 2021, with the reformatting of the form, information on gender and age became available. In 2021, 65% of the suspected ADR reports were for female patients, with an average age of 52 years. In 2022, the average age was 56 years. In 2023, 61% of the suspected ADR reports involved female patients, with an average age of 55 years.

Figure 3 also shows the total spontaneous suspected ADR reports, antineoplastic-related reports, and the percentage of spontaneous suspected ADR reports for antineoplastic drugs sent to the Pharmacovigilance Program of the university hospital in Porto Alegre from 2020 to 2023. In 2020, the Pharmacovigilance Program received 71 reports involving antineoplastic ADR, representing 59.7% of the total reports received. In 2021, reports of adverse reactions involving antineoplastics represented 47% (n=49) of the reports received. In 2022, the number of reports received further decreased to 24, representing 37% of the total reports received that year.

Discussão

The profile of spontaneous reports of antineoplastic ADR sent to the Pharmacovigilance Program of a university hospital in Porto Alegre in 2020 and 2021 was recently demonstrated, highlighting the importance of the integration and performance of the Pharmacovigilance Program with the healthcare team working in the hospital's[6] antineoplastic chemotherapy area. Based on the published results, this study continued the project by evaluating the impact of the Pharmacovigilance Program's activities on antineoplastic ADR reports at the university hospital.

It is important to note that in the previous study, approximately 90% of the recorded reports came from outpatients[6]. Thus, the results presented in Table 1 corroborate the findings of the previous study, showing that the majority of antineoplastic drug prescriptions made at the university hospital in Porto Alegre in this study were from the chemotherapy outpatient clinic, representing approximately 65% of the total antineoplastic chemotherapy prescriptions during the analyzed period. Similarly, it was shown that from 2020 to 2023, most of the spontaneous suspected ADR reports for antineoplastics sent to the Pharmacovigilance Program at the university hospital in Porto Alegre originated from the chemotherapy outpatient clinic, representing an annual average of 92%.

Figure 3. Number of total spontaneous suspected ADR notifications, of antineoplastics, and percentage (%) of spontaneous suspected ADR notifications of antineoplastics forwarded to the Pharmacovigilance Program of a university hospital in Porto Alegre from 2020 to 2023.

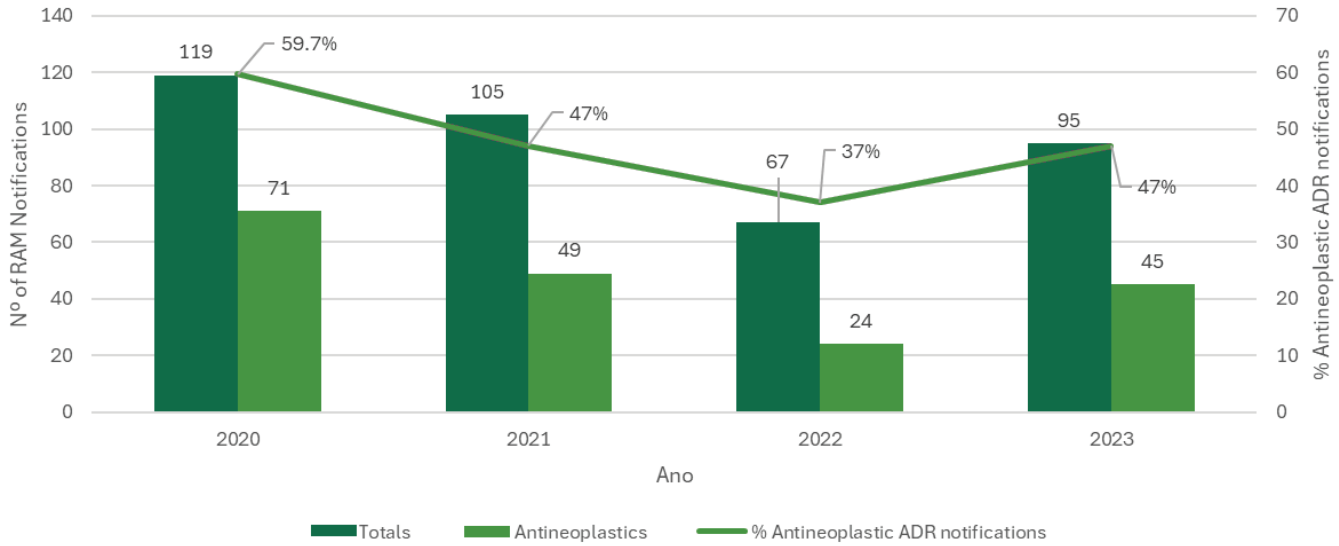


Table 2. Number of spontaneous reports of suspected adverse drug reactions (ADRs) to antineoplastic drugs submitted to the Pharmacovigilance Program of a university hospital in Porto Alegre from 2020 to 2023, originating from the chemotherapy outpatient clinic and inpatient department.

Nº of Reports of Adverse Drug Reactions (ADRs) to Antineoplastic Drugs (%)	2020	2021	2022	2023
Chemotherapy Outpatient Clinic	65 (91.5)	48 (98)	21 (87.5)	41 (91)
Inpatient Unit	6 (8,5)	1 (2)	3 (12,5)	4 (9)
Total	71 (100)	49 (100)	24 (100)	45 (100)

The above-mentioned data highlights the relevance of monitoring and reporting adverse events in outpatient care settings, emphasizing the need for a comprehensive approach to ensure the safety and quality of care provided to this specific population. In this context, it was possible to verify the total number of spontaneous reports of suspected ADRs overall, of antineoplastics, and the percentage of spontaneous reports of suspected ADRs of antineoplastics forwarded to the Pharmacovigilance Program of a university hospital in Porto Alegre from 2020 to 2023. In 2020, the Pharmacovigilance Program received 71 reports involving antineoplastic ADR, representing 59.7% of the total reports received. In 2021, reports of adverse reactions involving antineoplastics accounted for 47% (n=49) of the reports received. In 2022, the reports received saw an even greater reduction, with 24 reports, representing 37% of the total reports received in the year.

Regarding the year 2023, an increase was observed in both the number of total spontaneous reports of suspected ADR (n=95) and those of antineoplastics (n=45), consequently raising the percentage of spontaneous reports of suspected ADRs of antineoplastics (47%) forwarded to the Pharmacovigilance Program of the aforementioned university hospital. These are expected variations since the Pharmacovigilance Program closely collaborates with the chemotherapy outpatient team, constantly reinforcing the importance of recording reports as a motivational strategy, discussing process safety linked to the receipt of the notification analysis with pre-medication suggestions for the next cycle. This is an educational intervention originating from spontaneous reporting.

Thus, professionals working in the hospital's antineoplastic chemotherapy area are continuously encouraged to be attentive to occurrences of suspected ADR, naturally increasing the number of reports forwarded to the Pharmacovigilance Program. It is important to note that, upon observing the increase in the number of suspected ADR reports related to antineoplastics, discussion groups were held with 7 nursing staff members, involving shifts where antineoplastic therapy administration occurs. Through these discussions, feedback indicated that the team felt more secure in reporting, considering the receipt of analysis with pre-medication guidance or management for the patient's next chemotherapy cycle.

National and international scientific literature supports the data presented in this study, confirming the importance of pharmacovigilance activities[6,8,9], especially in the oncology field[6-16], contributing to increased patient safety. For example, a study characterizing reports in an oncology hospital in Porto Alegre analyzed 861 reports from 2018 to 2020, where incidents with harm were prevalent, corresponding to 87.3% of reported occurrences, with ADR during this period mostly related to antineoplastic drugs[11]. Additionally, demographic data were observed in this study, with the average age of these patients being 57.3 years, predominantly female, as the most affected by safety incidents, corresponding to 62.7%[11], a scenario very similar to the one presented in this work.

Another study also confirmed the importance of monitoring patients undergoing oncological treatment through the use of pharmacovigilance resources, which contributed to increased pharmacotherapy safety[9]. Similarly, a Portuguese study applied active pharmacovigilance in patients under treatment with oral antineoplastic agents, with multidisciplinary collaboration to improve early identification of adverse drug events, introducing the recent concept of additional monitoring to increase the number of suspected ADR reports, especially for drugs with limited safety data[18]. Furthermore, in 2020, a study was conducted in Nepal to evaluate the impact of an educational intervention on the knowledge and attitudes of healthcare professionals linked to a regional Pharmacovigilance center in an oncology hospital[22]. According to the authors, the effectiveness of a Pharmacovigilance program can be determined by the active involvement of healthcare professionals, their knowledge, attitude, and practice. Education and training programs can elevate the level of knowledge, attitude, and practice of healthcare professionals concerning Pharmacovigilance and ADR reporting[22].

In this context, it is essential to encourage pharmacovigilance actions, especially for drugs whose long-term effects are still unknown or in specific population groups, such as oncology patients. A quality investigative process is fundamental for decision-making in pharmacovigilance, fostering corrective and preventive actions[1]. However, this is not always the scenario in some institutions. For example, a study evaluating pharmacovigilance reports in a sentinel oncology hospital in Paraíba found a need for more investment in this area, particularly regarding the awareness of the importance of reporting to obtain data for regulatory purposes and ensure user safety[12].

Although spontaneous or voluntary reporting is the primary source of information for pharmacovigilance systems in generating hypotheses about possible ADR and is low cost, this reporting method has limitations related to high underreporting rates[1]. Thus, this was a limitation of the study in question, as well as other causes involved in underreporting already mentioned in the literature, such as a lack of knowledge about what an ADR is and its impact, the importance of reporting and how to do it, lack of time to fill out the report, and fear of punishment[13-16].

Another limitation identified during the work process evaluated was the need for joint action by the clinical pharmacist of the chemotherapy outpatient clinic with the follow-up of each analysis carried out by the Pharmacovigilance Program with pre-medication suggestions for the next chemotherapy cycle and the adherence of the care team to the medication inclusion interventions carried out before the administration of the antineoplastic drug. As institutional monitoring, the rate of severe adverse reactions is monitored monthly, with a target set at < 0.35 per 1000 patients per day. During the study period, there were no records of exceeding the institutional target. Additionally, another limitation of this work was the use of retrospective data from the Pharmacovigilance Program database of the Clinical Pharmacy section of the aforementioned university hospital, as this is not

restricted to just one professional, which can also be a weakness regarding access by other professionals, despite them receiving training to access the tool.

Conclusão

This study allowed the evaluation of the impact of the Pharmacovigilance Program on the reports of antineoplastic ADR in a university hospital in Porto Alegre and the verification of changes in the data on suspected ADR reports of antineoplastics received from the chemotherapy outpatient clinic with a differentiated performance of the said Program. The monitoring of antineoplastic reports received in this service demonstrated the need to formulate a detailed strategy to return to the notifier with an educational objective in conjunction with the chemotherapy outpatient clinic professionals and the care area involved in the notifications. From 2020 to 2022, there was a 66% reduction in reports received by the Pharmacovigilance Program involving antineoplastics, evidencing the importance of a more active Pharmacovigilance approach, contributing to medication safety in the hospital environment. Considering the results and the increase in the number of reports in 2023, it is extremely important not only to monitor the Pharmacovigilance Program but also to approach the care team to understand their perception and the factors involved in the increased notifications, as discussed.

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Conflict of Interest Statement

The authors declare no conflicts of interest regarding this article.

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