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Incident safety reports on generic and branded docetaxel medications in a teaching hospital

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Abstract

Objective: To compare incident reporting associated with generic and branded docetaxel in a Brazilian teaching hospital, and to analyze the pharmacovigilance notifications involving this drug in a teaching hospital. **Methods:** A cross-sectional study was conducted in a high complexity Brazilian university hospital. Data from patients aged 18 years or older were included. Incidents associated with docetaxel 80 mg reported in the hospital's pharmacovigilance database from January 1st, 2018, to December 31st, 2020, were analyzed. Reports of adverse drug reactions (ADR), therapeutic ineffectiveness, medication errors, and quality deviations (QD) were considered. Additionally, the underreporting rate of late ADRs was calculated. For descriptive analysis it was used the number of cases and percentages for categorical variables; and mean and standard deviation (SD) for continuous variables. **Results:** 124 incident reports related to chemotherapeutic agents were recorded. Among these, 34 (27.4%) were associated with docetaxel. Two involved the generic medication, while 32 were associated with the branded medication. Despite having a well-established multidisciplinary team in the oncology department, the most frequent reporters were nurses (26/34). The reports described 35 incidents: 21 ADR (10 immediate and 11 delayed) and 14 QD. Nine immediate ADR, 11 delayed ADR, and 12 QD reports were related to branded medication. The underreporting rate was 93.0%. **Conclusion:** Underreporting hindered the comparison of incidents associated with generic and branded docetaxel in the pharmacovigilance database. The lack of medication safety communication decreases signal detection and compromises decision-making rely on real-world data. In this regard, the findings suggest the need for educational interventions for healthcare professionals to improve attitudes towards pharmacovigilance.

Key-words: docetaxel; drugs, generic; pharmacovigilance; oncology service, hospital.

Notificações de incidentes de segurança relacionados ao docetaxel genérico e referência em um hospital de ensino

Resumo

Objetivo: Comparar as notificações de incidentes associados ao docetaxel genérico e de marca ou de referência em um hospital universitário brasileiro e analisar os dados de farmacovigilância envolvendo este fármaco em um hospital universitário. **Métodos:** Foi conduzido um estudo transversal em um hospital universitário brasileiro de alta complexidade. Foram incluídos dados de paciente com idade igual ou superior a 18 anos. Analisou-se incidentes associados ao docetaxel 80 mg notificados no banco de dados de farmacovigilância do hospital citado, de 1º de janeiro de 2018 a 31 de dezembro de 2020. Notificações de reações adversas a medicamentos (RAM), inefetividade terapêutica, erros de medicação e desvios de qualidade (DQ) foram consideradas. Ademais, calculou-se a taxa de subnotificação de RAM tardia. Para a análise descritiva, foram utilizados o número de casos e porcentagens para variáveis categóricas, e a média e o desvio padrão (DP) para variáveis contínuas. **Resultados:** Foram registadas 124 notificações de incidentes relacionados com agentes quimioterápicos. Entre estes, 34 (27,4%) estavam associados ao docetaxel. Dois envolveram o medicamento genérico, enquanto 32 foram associados ao medicamento de referência. A despeito de haver uma equipe multiprofissional consolidada no setor de oncologia, os notificadores mais frequentes foram os enfermeiros (26/34). As notificações descreveram 35 incidentes: 21 RAM (10 imediatas e 11 tardias) e 14 DQ. Nove notificações de RAM imediatas, 11 de RAM retardadas e 12 de DQ estavam relacionadas com medicamentos de marca. A taxa de subnotificação foi de 93,0%. **Conclusão:** A subnotificação limitou a comparação dos incidentes associados ao docetaxel genérico e de marca na base

de dados da farmacovigilância. A falta de comunicação relacionada à segurança dos medicamentos diminui a deteção de sinais e compromete a tomada de decisões com base em dados do mundo real. Nesse sentido, os achados sugerem a necessidade de intervenções educacionais para os profissionais de saúde, a fim de melhorar as atitudes em relação à farmacovigilância.

Palavras-chave: docetaxel; medicamentos genéricos; farmacovigilância; serviço hospitalar de oncologia.

Introduction

Docetaxel is a semi-synthetic derivative more potent than paclitaxel, whose active ingredient is isolated from *Taxus baccata*, a tree known as the Yew, from which the term taxanes for these drugs is derived[1]. It is available for commercialization as both a branded medication and a generic injectable medication in a dosage form of 80 mg for the treatment of breast cancer, non-small cell lung cancer, ovarian cancer, prostate cancer, stomach cancer, head and neck cancer, esophageal cancer, and uterine cancer[1].

According to Brazilian legislation Collegiate Board Resolution- RDC n° 16, of march 2nd 2007, for a medication to be registered as generic, it is necessary to demonstrate its pharmaceutical equivalence and bioequivalence (same bioavailability) in relation to the branded medication. Although formulations and manufacturing processes may not be identical, the differences should not compromise the necessary equivalence between the products. Thus, both can be considered therapeutic equivalents, since the medicines exhibit the same clinical efficacy and potential to cause adverse drug reactions (ADR)[2].

For most medicines available on the market, the bioequivalence limit ranges between 80.0% to 125.0%, which may be too wide for a standard 90% confidence interval[3]. However, for medicines with narrow therapeutic range, such as docetaxel[4,5], the limit of variation of the area under the curve of a concentration *versus* time graph is adjusted to 90-111.11% according to the Brazilian legislation Collegiate Board Resolution- RDC n° 742, of august 10th 2022. A medicine has a narrow therapeutic range when there is less than a two-fold difference in the minimum toxic and minimum effective plasma concentrations[6].

There is evidence that differences in the formulations of generic docetaxel may contribute to a higher incidence of incidents, such as quality deviations, therapeutic failure, and ADR[4]. The presence of impurities, low active ingredient content, dosage form (dry powder for injection), packaging specifications[7] and under control over the (pseudo)polymorphic forms of the active pharmaceutical ingredient during both development and the entire product lifecycle also impact on safety, efficacy and quality of the medication[5]. Despite international data showing a higher frequency of febrile neutropenia associated with generic docetaxel[3], in Brazil, Tarcha et al.[8] identified the branded medication as a risk factor for the occurrence of the ADR using data obtained from electronic medical records of patients treated at a cancer center.

Regardless of how the drug was registered (brand or generic drug), pharmacovigilance studies involving antineoplastic agents are relevant, considering their unfavorable safety profile. Two studies conducted in Brazilian hospitals showed that adverse event reports were more frequent among antineoplastic drugs[9,10]. In turn, studies carried out in pharmacovigilance databases represent a viable and applicable strategy for oncology signal screening[11], aided by the development of machine learning algorithms[12]. A signal in pharmacovigilance consists of a set of data that suggests a relationship between a drug and an adverse event, so the initial hypothesis is followed by data, assessments, and arguments[13,14].

High prevalence of serious ADR related to taxanes were reported in the Brazilian Health Regulatory Agency (Anvisa) spontaneous reporting system, which were most frequently associated with docetaxel[11].

Post-commercialization surveillance of oncological treatment is required to contribute to risk management and market regulation. There are limitations in the quality control and bioequivalence testing of docetaxel. In this context, real-world studies that assess the toxicity profile of antineoplastic drugs and compare the safety of generic and brand-name formulations should be encouraged, since pre-marketing studies have restrictions regarding their conduct and participant inclusion[3]. However, to the best of our knowledge, there is no studies in pharmacovigilance databases that have compared the incidents reported for branded and generic 80 mg docetaxel. In this setting, the study aimed to compare the incident reports associated with generic and branded use of docetaxel in a Brazilian teaching hospital.

Methods

Study design

A cross-sectional study involving the analysis of incidents associated with dosage form of 80 mg docetaxel reported in the pharmacovigilance database of the Teaching Hospital of the Medical School of Ribeirão Preto, University of São Paulo, Brazil, was conducted from January 1st, 2018, to December 31st, 2020. The report was based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[15].

Setting

The pharmacovigilance database of the hospital includes electronic spontaneous incidents reporting (ADR, quality deviations, suspicious of therapeutic ineffectiveness and medication errors), which are notified by health professionals.

The incidents related to the medicines are assessed for a pharmacist of the risk management to carry out causality imputation (definite, probable, possible or impossible). After the evaluation, the cases with causality ≥ possible are reported to the Brazilian System of Pharmacovigilance (Vigimed).

The Hospital of the Medical School of Ribeirão Preto was pioneering in activities related to pharmacovigilance at Brazil. Since 2002, the hospital has been part of the Sentinel Network, which supports the National Health Surveillance System by providing reports of adverse events and quality deviations regarding technovigilance, pharmacovigilance, hemovigilance, among others. The health assistance provided by the institution covers, on average, 3.5 million inhabitants.

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Participants

The incident reports from the hospital´s pharmacovigilance database was retrospectively analyzed. The selection period was January 1st, 2018, to December 31st, 2020. The reports of all patients aged ≥ 18 years, who received the prescription and administration of the dosage form of 80 mg docetaxel (generic or branded medications) were included in the study.

Incident was defined as an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient[16]. In the present study, ADR, and drug related problems without harm (such as medication errors and quality deviations) were considered incidents.

Variables

The primary predictor of the study was the comparison of incident reporting between generic and branded dosage form of 80 mg docetaxel. The secondary predictor was the underreporting rate. Therefore, the following variables were extracted:

a) Number of patients who used the dosage form of 80 mg docetaxel.

b) Number of patients with incidents associated with the dosage form of 80 mg docetaxel documented in medical record.

c) Number of patients who had incidents associated with dosage form of 80 mg docetaxel reported to the pharmacovigilance database of the hospital.

d) Number of incidents associated with the antineoplastic medications reported to the pharmacovigilance database of the hospital.

e) Number of incidents associated with the dosage form of 80 mg docetaxel reported:

1. Demographic characteristics of patients (gender and age);
2. Clinical history of patients (health conditions and comorbidities);
3. Etiology of the incident (ADR, therapeutic ineffectiveness, quality deviation, and medication errors);

i. Health professional responsible for the reporting.

ii. ADR reports: clinical manifestations, classification according to the time of occurrence (immediate or delayed), management, dechallenge and rechallenge, dosage form of 80 mg docetaxel (generic or branded medication).

iii. Therapeutic ineffectiveness reports: posology, number of cycles, concomitant pharmacotherapy, dosage form of 80 mg docetaxel (generic or branded medication).

iv. Quality deviation: technical complaints reported, dosage form of 80 mg docetaxel (generic or branded medication).

v. Medication errors: discrepancies observed during the medication use process (prescription, distribution, compounding practices, administration) and institutional guidelines.

Data collection

The screening of incident reports performed by healthcare professionals was carried out using the Brazilian nonproprietary name for pharmaceutical substances of the selected antineoplastic medications at the hospital under study (Table 1). For healthcare establishments within the Unified Health System (SUS), such as the Hospital of the Medical School of Ribeirão Preto, the Brazilian nonproprietary name or, in its absence, the International Nonproprietary Name (INN) for pharmaceutical substances had to be adopted according to the Brazilian legislation Collegiate Board Resolution - RDC n° 51, of august 15th 2007. The variables of interest were extracted for the reports involving docetaxel.

The electronic prescription system was screened to recruit patients who used dosage form of 80 mg docetaxel. For these patients, the electronic medical record was reviewed to enroll those who met the inclusion criteria and then verify the presence of documentation of healthcare professionals regarding the occurrence of incidents related to the use of the medications of interest.

The inventory management system was also consulted to identify the batch, manufacturer, and dosage form of 80 mg docetaxel (generic or branded), according to the availability of the products during the data collection period. The dates from the management system were compared with the dates of the reports to establish whether the occurrence of the observed incident was associated with the branded or generic medication.

In the present study, branded medication was considered the original, innovative, or reference product. Immediate ADR was considered those which occurred until three days after drug administration; and delayed ADR those which started after the fourth day[17].

Findings obtained from each dosage form of 80 mg docetaxel were compared to verify differences in the occurrence of incidents and to identify which medication (generic or branded) is considered safer, more effective, and associated with a lower frequency of incidents.

Owing to assess the delayed ADR underreporting rate, the following equation was applied:

$$\textit{Underreporting rate:} \quad \frac{\textit{patients with incidents documented in medical records} - \textit{patients with incident reported}}{\textit{Patients with incidents documented in medical records}}$$

Study size

The study included all patients who used the dosage form of 80 mg docetaxel during the analyzed period, as well as all spontaneously incidents reports performed by health professionals between January 1st, 2018, and December 31st, 2020, which were associated with antineoplastic medications.

Statistical methods

For descriptive analysis it was used the number of cases and percentages for categorical variables; and mean and standard deviation (SD) for continuous variables.

Ethical Approval:

The present study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments and approved by the Research Ethics Committee (CEP) of the School of Pharmaceutical Sciences of Ribeirão Preto-University of São Paulo) (FCFRP/USP) on 02/12/2020 (protocol number: 4.434.494- CAAE: 30739020.6.0000.5403).

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Results

During the study period, incidents related to the use of 20 different antineoplastic drugs were reported to the hospital's pharmacovigilance database. The drug with the highest number of reported incidents was docetaxel, which is the focus of this study. Regarding docetaxel, 503 patients had administered the dosage form of 80 mg docetaxel, of which the majority were female [78.7% (396)] and adults up to 59 years old [55.9% (281/503)]. Most of them used the branded medication [55.1% (277)], followed by generic medication [24.2% (122)]; and both dosage forms [20.7% (104)].

According to medical record review, 490 patients who used docetaxel developed ADR: 444 developed only delayed ADR; two only immediate ADR, and 44 both. Regarding the medications, 24.3% (n=119) of patients developed ADR arising from generic medication; 54.7% (n=268) related to branded medication; and 21.0% (n=103) associated with both dosage forms.

Health professionals reported 124 incidents associated with antineoplastic medications to the hospital's pharmacovigilance database. Most reports were related to ADR [83.1% (103/124)], mainly due to docetaxel (Table 1). The reports related to 80 mg docetaxel (n=34) recorded in the hospital's pharmacovigilance database was done for 20 patients; and described 35 incidents. Most of patients were female (n=17). The commonest diagnosis was breast cancer (n=17). Among the professionals who are part of the healthcare team, nurses are the ones who reported the most incidents (26/34) (Table 2). Considering only ADR reports, nurses reported 95.2% of the cases (20/21).

The 21 ADR reports described 14 different signs and symptoms that were possibly related to docetaxel. No observed clinical manifestations were serious. Ten occurred during chemotherapy infusion (flushing of the face/neck/ears/chest, back/lower back/chest pain, cough/sore throat, malaise, dyspnea, sensation of throat closing/choking) and 11 were delayed (itching, lesions in the venous route area, peeling lesion at the administration site, and peeling of the skin on the back of the hand/wrist).

Regarding the reports containing the management of immediate ADR (n=10), all patients had chemotherapy withdrawn after the detection of signs and symptoms. Among these, seven also required treatment with hydrocortisone as monotherapy or in combination, and one patient was treated with promethazine, salbutamol, and ipratropium bromide. Two patients with immediate ADR described as flushing of the face/neck/chest, sensation of throat closing, and back/chest pain did not require pharmacological management. After resolution of immediate ADR, chemotherapy was reintroduced without positive rechallenge for eight patients (the ADR did not reappear when treatment was restarted). Chemotherapy was permanently discontinued in two patients. Of these, one complained of lower back pain, facial flushing, and aphonia, while the other reported pain at the venous site, cough, sore throat, dyspnea, and choking sensation.

Among the eleven patients who experienced only delayed adverse drug reactions (ADRs), five (45.5%) did not have their management reported. Six patients (54,5%) received non-pharmacological interventions to prevent cutaneous toxicity, such as health literacy to avoid sun exposure, use sunscreen and moisturizer. The mean interval between medication infusion and symptom onset was 9.5 days (±6.5). There was a lack of information related to rechallenge for patients with delayed ADR.

Thirteen reports were related to quality deviation reports. These documents described 14 different complaints: precipitation of the medication after dilution or during infusion (n=7), change in the color of the intravenous drip chamber (n=2), cloudiness of the solution (n=2), inappropriate sealing of the vial ampoule (n=1), vial of medication broken inside the packaging (n=1), and vial appearing to contain remnants of medication on the outside without signs of breakage (n=1).

Two reports that described two incidents were associated with generic medication (2/34), with one of them referring to immediate ADR and the other related to quality deviation. The remaining 32 reports (32/34) were associated with branded medication, of which nine described immediate ADR, 11 delayed ADR, and 12 quality deviations.

Delayed ADR underreporting rate was 93.0%. Regarding the dosage forms of 80 mg docetaxel, the ADR underreporting rate on pharmacovigilance database was 98.3% for generic medication, while for branded medication was 88.1%. We excluded the group that used both forms, as it was not possible to attribute whether the ADR arose from generic or branded docetaxel.

Table 1. Incident safety reports associated with antineoplastic medications, according to the etiology, reported to the hospital's pharmacovigilance database.

Antineoplastic medication	Incident reports n (%)	Etiology of the incidents	
		ADR reports n (%)	QD reports n (%)
docetaxel 80.0 mg	34 (27.4)	21 (20.4)	13* (61.9)
paclitaxel 300.0 mg	24 (19.4)	23 (22.3)	1 (4.8)
carboplatin 450.0 mg	21 (16.9)	21 (20.4)	0 (0.0)
oxaliplatin 100.0 mg	20 (16.1)	19 (18.4)	1 (4.8)
doxorubicin 50.0 mg	5 (4.0)	4 (3.9)	1 (4.8)
methotrexate 50.0 mg	3 (2.4)	3 (2.9)	0 (0.0)
cisplatin 100.0 mg	2 (1.6)	1 (1.0)	1 (4.8)
etoposide 100.0 mg	2 (1.6)	1 (1.0)	1 (4.8)
cetuximab 100.0 mg	2 (1.6)	2 (1.9)	0 (0.0)
cisplatin 50.0 mg	1 (0.8)	1 (1.0)	0 (0.0)
ifosfamide 1,000.0 mg	1 (0.8)	0 (0.0)	1 (4.8)
ifosfamide 2,000.0 mg	1 (0.8)	1 (1.0)	0 (0.0)
fluorouracil 2.5 g	1 (0.8)	1 (1.0)	0 (0.0)
methotrexate 5.0 g	1 (0.8)	1 (1.0)	0 (0.0)
dactinomycin 0.5 mg	1 (0.8)	0 (0.0)	1 (4.8)
idarubicin 10.0 mg	1 (0.8)	0 (0.0)	1(4.8)
bortezomib 3.5 mg	1 (0.8)	1 (1.0)	0 (0.0)
rituximab 500.0 mg	1 (0.8)	1 (1.0)	0 (0.0)
trastuzumab 150.0 mg	1 (0.8)	1 (1.0)	0 (0.0)
pegaspargase 3,750.0 UI	1 (0.8)	1 (1.0)	0 (0.0)
TOTAL	124 (100.0)	103 (100.0)	21 (100.0)

ADR= adverse drug reaction. QD= quality deviations. *One QD report recorded two QD incidents (total number of incidentes = 14).

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Table 2. Characteristics of incident safety reports associated with docetaxel use reported to the pharmacovigilance database of the hospital

Variables	n (%)
Demographic and clinical characteristcs of the patients	
Gender	
Male	3 (15.0)
Female	17 (85.0)
Total	20 (100.0)
Age	
Adults (18-59 years)	10 (50.0)
Older people (≥ 60 years)	10 (50.0)
Total	20 (100.0)
Cancer diagnoses	
Breast	17 (85.0)
Prostatic	2 (10.0)
Lung	1 (5.0)
Total	20 (100.0)
Health professional	
Nurses	26 (76.5)
Pharmacists	7 (20.6)
Physicians	1 (2.9)
Total	34 (100.0)
Etiology of the incidents reports	
ADR	21 (61.8)
Quality deviation	13 (38.2)
Total	34 (100.0)
ADR reports	
Signs and symptons onset	
Immediate	10 (4.7)
Delayded	11 (52.4)
Total	21 (100.0)
Pharmacological management	
Yes	8 (38.1)
No	2 (9.5)
Not reported	11 (52.4)
Total	21 (100.0)
Rechallenge	
Yes	8 (38.1)
No	2 (9.5)
Not reported	11 (52.4)
Total	21 (100.0)
Positive Rechallenge	
Yes	0 (0.0)
No	8 (38.1)
Not reported/ not re-exposed to the drug	13 (61.9)
Total	21 (100.0)
Types of quality deviation incidents reported	
Organoleptic changes	11 (76.9)
Packaging/bottle complains	3 (23.1)
Total	14* (100.0)

ADR= adverse drug reaction. *One QD report recorded two QD incidents (total number of incidentes = 14).

Discussion

The advancement of computer science has contributed to increasing the capacity to extract information about the safety of medication use and generate pharmacovigilance signals that might impact public health policies, pharmaceutical market regulation, and clinical decision-making[18]. Especially for injectable medications with a narrow therapeutic range, the quality, safety, and effectiveness of medications directly affect patients' lives[3,19].

Studies has been demonstrating that the number of reports in pharmacovigilance databases associated with generic medications is lower when compared to those performed for the branded medication[20-23]. This is likely due to the greater familiarity of both providers and consumers with the manufacturer's brand name rather than the INN[21].

However, there is no consensus in the literature regarding signal generation. Wang et al.[20] observed that for brand-name medications, the signal was lower. However, Desai et al.[24] concluded that clinical outcomes were similar regardless of the forms. Owing to signal detection depends on the quantity and quality of spontaneous reporting[25-27], the quality of pharmacovigilance databases relies on how patients and healthcare providers recognize and report their medications, as well as how manufacturers collect and follow up on reported adverse events with their products[21].

For antineoplastic medications, ADR underreporting likely occurs since adverse events induced by these medications are often considered normal or inevitable[11]. Issues related to completeness (such as missing data) have long been recognized as significant factors impeding the usefulness of existing individual case report data[31]. While most signals were supported by temporality (time to onset) and dechallenge/rechallenge, clear reporting of judgments on causality remains infrequent[28,29]. Additionally, Bohn et al.[23] found that the suspect product type (brand or generic) could not be determined for the majority of the reports.

Owing to prevent underreporting, pharmacovigilance stakeholders should act to promote more detailed reporting practices[23], as well as the utilization of multiple sources of information and data, in addition to pharmacovigilance database to identify risks and developed strategies to minimize them[22]. In hospital settings, the primary purpose of spontaneous reporting is to contribute to promote patient safety through comprehensive assessment, risk communication and safe prescribing[30]. However, in Brazil, oncological ADR reporting needs to be encouraged, due to the lack of attitude of health professionals[31]. Mainly for physicians who, despite the better quality of information provided[28], they are the least knowledgeable toward pharmacovigilance activities[32].

The demographic characteristics of patients and ADR identified in the pharmacovigilance database of the present study were similar to those detected in the ANVISA spontaneous reports system[11] and in pharmacoepidemiological studies conducted at other hospital institutions[8,31,33]. Although Tarcha et al.[8] evidenced a higher frequency of febrile neutropenia in patients using generic docetaxel with cyclophosphamide in a retrospective chart review study, the authors did not observe a statistically significant difference in the 5-year progression-free survival when comparing the two medications. Although generic drugs are a recognized alternative to improving access to medicines worldwide, some authors suggest that caution should be exercised when prescribing a generic drug or recommending the substitution of a brand-name drug with a generic one in cases involving medications with a narrow therapeutic index, such as antiepileptic drugs or immunosuppressants [34,35].

Despite our findings showing a greater number of incident reports associated with branded docetaxel, the underreporting impaired to determine which is considered safer, more effective, and of better quality. Furthermore, since the data collection was conducted in a hospital setting, incident reporting may differ from unreported cases in terms of seriousness. The findings represent a single hospital pharmacovigilance database with its own characteristics, which may introduce bias and make it difficult to extrapolate the results and compare them with pharmacovigilance spontaneous reporting systems from other hospitals.

Nevertheless, the study has strengths, as it was the first to compare generic and branded docetaxel using a hospital pharmacovigilance database. Moreover, the findings suggest the need for educational interventions for healthcare professionals to improve attitudes towards pharmacovigilance, the quality of information of the reports, and the use of both passive and active post-marketing methods to contribute to pharmacotherapeutic decision-making among oncological patients.

Conclusion

One out of 24 patients with incidents documented in medical records had the case reported to the institutional pharmacovigilance database. The underreporting rate impaired the comparison of safety, efficacy, and quality of generic and brand-name docetaxel medications.

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Collaborators

1. Project conception or analysis and interpretation of data: L.H.R., F.R.V., L.R.L.P., F.M.P.

2. Article writing or critical review relevant to the intellectual content: L.H.R., L.R.B., V.P.P.V, F.M.P., L.M.V., G.R.V., J.P.V.R, L.R.L.P., F.R.V.

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Declaration of conflicting interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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