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Observational study of clinical toxicity with different formulations of docetaxel in breast cancer patients

Estudio observacional de la toxicidad con diferentes formulaciones de docetaxel en pacientes con cáncer de mama

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Abstract

Objective: To analyze the excipients and impurities contained in the various docetaxel products available on the market and find out whether they may be responsible for any of the different adverse events associated with the use of docetaxel in patients with breast cancer receiving adjuvant or neoadjuvant treatment.

Method: This is a prospective, multicenter, longitudinal observational, study carried in 26 hospitals in Madrid, Catalonia, Andalusia, and the Valencia Region. The different docetaxel formulations were characterized in terms of their pH, amount of the active ingredient and impurities. The cumulative incidence of adverse events of any grade was evaluated. Adverse events were stratified by drug type and differences were analyzed by means of a chi-square test.

Results: Statistically significant differences were found between the different docetaxel formulations in the cumulative per-cycle incidence of: dosage change, anemia, hypersensitivity reactions and anaphylaxis, neuropathy, palmoplantar and dermal toxicity, ungual toxicity and facial

Resumen

Objetivo: Estudiar los excipientes e impurezas de los diferentes medicamentos comercializados de docetaxel y conocer la incidencia de los diversos eventos adversos derivados del uso de docetaxel y su repercusión clínica en pacientes con cáncer de mama en el contexto de adyuvancia o neoadyuvancia.

Método: Estudio observacional, longitudinal, prospectivo y multicéntrico en 26 hospitales de Madrid, Cataluña, Andalucía y Comunidad Valenciana. Se caracterizaron las distintas formulaciones de docetaxel en cuanto a pH, cantidad de docetaxel e impurezas. Se evaluó la incidencia acumulada de eventos adversos de cualquier grado estratificados por tipo de medicamento, analizando las diferencias mediante el test de χ^2.

Resultados: Se detectaron diferencias estadísticamente significativas entre las distintas formulaciones de docetaxel en cuanto a la incidencia acumulada por ciclo de: modificación de dosis, anemia, reacciones de hipersensibilidad y anafilaxia, neuropatía, toxicidad palmo-plantar y dermatológica, toxicidad ungueal y edema facial. La formulación con un

KEYWORDS
Docetaxel; Taxoids/adverse effects;
Generic drugs/adverse effects; Excipients; Breast cancer.

PALABRAS CLAVE
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edema. The formulation with the lowest content of impurities showed better results in terms of change of dosage, visits to the emergency room and incidence of anemia and facial edema. However, it was associated with poorer results regarding hospitalization, febrile neutropenia, motor neuropathy and palmoplantar toxicity.

Conclusions: The results of the study showed differences in the incidence of adverse events of the different docetaxel products available in Spain. Such differences were statistically significant for some of the variables analyzed. The study was not able to determine which of the products offered the best toxicity profile. Nor was it possible to establish a correlation with respect to the composition of excipients or the content of impurities.

menor contenido en impurezas presentó mejores resultados en modificación de dosis, visitas a urgencias, e incidencia de anemia y edema facial, pero peores en hospitalización, neutropenia febril, neuropatía motora y toxicidad palmo-plantar.

Conclusiones: Los resultados muestran diferencias en la incidencia de los eventos adversos de los distintos medicamentos con docetaxel comercializados en nuestro país, con diferencias significativas entre ellos en algunas de las variables estudiadas. No se ha podido identificar un medicamento con un mejor perfil de toxicidad. Tampoco se ha podido establecer su relación con respecto a la composición de excipientes e impurezas.

Introduction

Docetaxel is an antineoplastic agent that stimulates the assembly of tubulin, stabilizing microtubules, preventing their depolymerization and markedly reducing the levels of the free form of the protein. As a result, docetaxel inhibits mitotic spindle assembly during cell division, thus impeding the mitotic process[1,2]. Docetaxel is currently indicated in breast cancer, non-small-cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer, and is commonly administered in doses of 75-100 mg/m^2 every 3 weeks[2].

Generic drugs represent an excellent solution for curbing the skyrocketing costs of healthcare systems. Indeed, their price is lower than that of branded drugs as they do not require any research or development and there is fierce competition among manufacturers to introduce their different formulations into the market[3]. According to European Union legislation, a generic drug is "a medicine that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference pharmaceutical product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies". The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy[4,5]. In order to be approved by drug agencies, generic and innovative drugs must possess the same level of chemical-pharmaceutical quality and are required to submit the same documents and meet identical requirements.

Although the European Medicines Agency's (EMA) guidelines require bioequivalence studies to be performed for all orally-administered generics, such a requirement does not normally apply to generic aqueous parenteral solutions containing equal amounts of the active ingredient as the reference product. Should these generics contain excipients that interact with the active ingredient or otherwise affect the disposition of the active ingredient, a bioavailability study will be required, unless both the generic and the reference product contain similar amounts of the same excipients or it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active ingredient[6].

One concern about docetaxel is its poor aqueous solubility, which means it must be formulated with polysorbate 80 (Tween 80), a non-ionic surfactant, and ethanol. These excipients solubilize the drug, making it amenable to intravenous administration, ensuring its stability during storage, and preventing it from adhering to the walls of the vial or precipitating during the self-life of the formulation.

Article 34 of Spanish Royal Decree 1345/2007 stipulates that a drug's composition statement shall mandatorily include a list of the excipients used in its formulation, as an understanding of the nature of such substances may be necessary for correct use and administration of the drug. It also states that the list of excipients required to be declared on the label shall be updated in the light of scientific and technological advances, and in accordance with the dictates of the European Union. Annex III establishes that all excipients in injectable, ocular, and topical medicines must be disclosed.

The most widely used docetaxel drug is Taxotere®, a concentrate and solvent for solution for infusion produced by Sanofi-Aventis France[2]. It was approved through a centralized procedure and has been available in Europe since November 1995. The original 20 and 80 mg formulations contained two vials, one with docetaxel anhydrous solubilized in polysorbate, which contained 40 mg/dl docetaxel and 1,040 mg/ml polysorbate, and the other with a solvent (13% ethanol). The contents of the first vial had to be diluted 1:4 with the solvent prior to being transferred to the infusion bag. In 2009, in parallel with the appearance of generic docetaxel formulations, all drugs containing this active ingredient were reformulated. In the new formulation, a single vial contains the active ingredient together with all the excipients ready to be added to the solution to be administered. As a result of this change, the amounts of excipients also varied, particularly in the case of ethanol whose volume nearly doubled as compared with the original two-vial formulation.

Several studies have found that the varying amounts of polysorbate 80 and ethanol contained in the different docetaxel formulations could be associated with differences in the incidence of severely acute hypersensitivity reactions and skin toxicity, which set the clinical profile of such products apart from that of docetaxel's original formulation, comprising mainly irritative symproms[7]. A retrospective Canadian study showed that a specific generic formulation of docetaxel resulted in a similar number of severe hematologic adverse events to the original formulation in patients with breast cancer, although the former were more frequently affected by grade 4 febrile neutropenia and therefore needed longer hospitalization periods[8].

The main purpose of the present study was to analyze the excipients and impurities of the different docetaxel products available on the market and understand the incidence of the different kinds of adverse events resulting from their use as well as their clinical effect on patients with breast cancer receiving adjuvant or neoadjuvant treatment.

Methods

This is a prospective, multicenter, longitudinal observational, study carried out in 26 different hospitals from Madrid, Catalonia, Andalusia, and the Valencia Region. The study was promoted by the Spanish Oncologic Pharmacy Group (GEDEFO) and the Pharmacokinetics and Clinical Pharmacogenetic (PkGen) Group of the Spanish Society of Hospital Pharmacists (SEFH). The study was recognized by the Spanish Agency for Medicines and Medical Products as a prospectively planned post-authorization study (EPA-SP) and was approved by the research ethics committees of all participating hospitals. All patients were asked to sign an informed consent form. The recruitment period extended from November 2015 to October 2017, with patient follow-up being continued until the end of treatment.

The different docetaxel formulations were characterized in terms of their pH, amount of active ingredient and impurities by the PkGen group at the Clínica Universitaria de Navarra (CUN). As regards the excipients in the different docetaxel formulations, the amount of alcohol was obtained from the label of each product, and the amount of polysorbate 80 was reported by the different manufacturers. The chromatographic analysis of the different docetaxel products was performed in duplicate, with the exception of the Taxotere® 20 mg/mL vial, which was analyzed in quintuplicate and used as a reference. The chromatographic analysis was performed in acetic acid and acetonitrile to ensure that the composition of the samples was as similar as possible to the solvent used in the mobile phase of the chromatographic study, thus avoiding disruption in the chromatograms. Samples were analyzed using an Agilent 1200 system. Results were interpreted by means of the ChemStation (Agilent) software package.

The hospitals' oncological pharmacists participated in the recruitment of all the patients who met the inclusion criteria specified, in the collection of demographic and clinical data, and in the clinical evaluation of toxicity,

which was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of the National Cancer Institute.

To be included in the study patients had to have a diagnosis of early breast cancer and a score of 0 on the Eastern Cooperative Oncology Group (ECOG) scale; they had to be scheduled for adjuvant or neoadjuvant treatment with taxotere-cyclophosphamide (TC) (75 mg/m^2 taxotere and 600 mg/m^2 cyclophosphamide intravenously every 21 days up to a maximum of 4-6 cycles) or a sequential regimen of 4 cycles of 100 mg/m^2 taxotere following 4 cycles of adriamycin and cyclophosphamide (AC-T) intravenously every 21 days. Patients participating in clinical trials and those with liver enzyme counts (aspartate aminotransferase and/or alanine aminotransferase) higher than 1.5 times the upper limit of normal (ULN), alkaline phosphatase above 2.5 times ULN, and/or bilirubin above ULN were excluded from the study.

The variables considered included independent demographic variables such as age at diagnosis, weight, height, waist circumference and body mass index; disease-related variables (molecular subtype and date of surgery for cases of adjuvant treatment); treatment-related variables (mode of administration [in-patient vs. outpatient], chemotherapy regimen, dose, number of cycles, and premedication schedule); and medication-related variables. Variables dependent on the different docetaxel products analyzed included adverse events (the cycle at which they began, their duration and their intensity according to the CTCAE v4.0 grading system); toxicity-related hospitalizations and their duration; length of treatment, dose titration; reason for discontinuation, and use of colony-stimulating factors.

An electronic logbook was designed to facilitate online data collection. The information recorded in the patient's clinical record and in the pharmacy department's prescription and dispensing systems was used as a basis. Patients were interviewed at each treatment cycle to determine the presence of any toxicities.

A data management plan was designed to export the information in the electronic logbook to a medium where it could be statistically processed using the IBM SPSS Statistics for Windows version 21.0 software package. A descriptive analysis was conducted using measures of central tendency and dispersion for quantitative variables. Qualitative variables were reported as frequency distributions. The cumulative incidence of adverse events was calculated with their respective confidence intervals (95%). Adverse events were analyzed for the different docetaxel drug products, comparing differences between them with the chi square test. Statistical significance was established at $p < 0.05$. An age-adjusted multivariate analysis was performed of adverse events as a function of treatment and dosing regimen.

Results

Tables 1 and 2 show the excipients included in the different docetaxel products available on the market, as well as the results of the chromatographic analysis of impurities, amount of active ingredient and pH, respectively.

The study included a total of 335 patients, all of them female except for 5 males. Mean age was 55.3 ± 11.2 years, mean weight was 74.8 ± 61 kg and mean body mass index was 27 ± 5.5 kg/m^2. Geographic distribution was as follows: 117 patients were from Madrid (34.9%), 95 from Catalonia (28.4%), 81 from Andalusia (24.2%) and 42 from the Valencia Region (12.5%). The purpose of chemotherapy was adjuvant in 73.4% of patients and neoadjuvant in 26.6%, with the majority of patients being chemotherapy naïve (89.9%). As regards the tumor phenotype, 83.9% of patients were hormone receptor-positive, as compared with 16.1% who presented with triple negative tumors. Even if being HER2-positive was an exclusion criterion, the sample included three HER2-positive patients given that their positivity was confirmed later by pathology evaluation.

Table 1. Excipients contained in the different docetaxel products used in the study*

Excipients	Docetaxel Actavis	Docetaxel Hospira	Docetaxel Accord	Taxotere®	Docetaxel Teva	Taxotere® (original)**	Docetaxel Sandoz
Ethanol (mg/100 mg docetaxel	2,000	1,820	1,975	1,975	< 500	925	2,562
Polysorbate (mg/100 mg docetaxel)	2,120	2,600	2,600	2,000	No data	2,600	800
Other excipients	Citric acid, povidone	Citric acid, PEG300	Citric acid	–	–	–	Citric acid, macrogol 300

*Some of these formulations may not be currently available in Spain.
**This product was available until 2009 as a two-vial formulation. After that, it was changed to the current one-vial formulation, which is similar to that of the other docetaxel products.

Table 2. Chromatographic study of impurities, amount of docetaxel, and pH of the products used in the study

Product	Total percentage of impurities*	Amount of docetaxel**	pH
Taxotere® Sanofi 20 mg/1 mL	0.71%	100%	3.87
Taxotere® Sanofi 80 mg/4 mL	0.74%	102%	3.95
Taxotere® Sanofi 160 mg/8 mL	0.72%	100%	3.83
Docetaxel Accord 20 mg/1 mL	1.34%	101%	4.01
Docetaxel Accord 80 mg/4 mL	1.05%	99%	3.95
Docetaxel Accord 160 mg/8 mL	0.95%	101%	4.12
Docetaxel Actavis 80 mg/4 mL	0.86%	99%	4.26
Docetaxel Actavis 140 mg/7 mL	0.87%	97%	4.01
Docetaxel Hospira 80 mg/8 mL	1.27%	98%	3.85
Docetaxel Teva 20 mg/0.72 mL	1.23%	102%	3.93
Docetaxel Teva 80 mg/2.88 mL	1.27%	103%	4.09

*Sum of the areas of all the impurity chromatographic peaks relative to the area corresponding to the docetaxel chromatographic peak, expressed as a percentage.
**Amount of docetaxel in the commercially available formulations, calculated with respect to the amount of docetaxel in Taxotere® 20, expressed as a percentage.

Table 3. Chemotherapy regimens and cycles administered using the docetaxel products analyzed in the study

	Docetaxel Actavis	Docetaxel Hospira*	Docetaxel Accord	Taxotere®	Docetaxel Teva	Total
Patients, *n* (%)	121 (36.1)	100 (29.9)	45 (13.4)	41 (12.2)	28 (8.4)	335
Chemotherapy regimen, *n* (%)						
AC-T	59 (48.8)	30 (30.0)	15 (33.3)	9 (22.0)	16 (57.1)	129 (38.5)
TC	62 (51.2)	70 (70.0)	30 (66.6)	32 (78.0)	12 (42.9)	206 (61.5)
Cycles administered, *n* (%)	460 (34.0)	444 (32.8)	181(13.4)	156 (11.5)	112 (8.3)	1,353

AC-T: Sequential use of docetaxel following adriamycin and cyclophosphamide; TC: docetaxel and cyclophosphamide regimen.
*Currently marketed by Pfizer.

Table 3 shows the rate of use of the different docetaxel products analyzed in the study and their distribution across the different treatment regimens administered. A comparison of the two chemotherapy regimens evaluated shows that the mean dose of docetaxel per cycle and m^2 under the AC-T regimen was statistically significantly higher than in the TC regimen (89.6 vs 74.6 mg/m^2; $p < 0.001$).

The percentage of patients where treatment with docetaxel was discontinued was 8.9%, i.e. 30 patients in total. In 28 of them discontinuation was mandated by drug-related toxicity. Table 4 shows the cumulative distribution of adverse events across the different docetaxel products. Statistically significant differences were observed between the different docetaxel products in terms of the per-cycle cumulative incidence of dosage changes, emergency room visits, anemia, hypersensitivity reactions and anaphylaxis, sensory and motor neuropathy, palmoplantar and dermal toxicity, ungual toxicity, and facial edema. As shown in table 4, each drug had different incidence rates. Specifically, Taxotere® exhibited statistically significant differences in terms of its lower incidence of dosage changes, visits to the emergency room, anemia and facial edema, and higher levels of neuropathy. The Accord formulation was associated with less neuropathy and palmoplantar and ungual toxicity, but higher rates of dosage changes and facial edema. Teva presented with fewer hypersensitivity reactions/anaphylaxis and motor neuropathy, but more ungual toxicity and sensory neuropathy. Hospira resulted in less dermal toxicity, and Actavis in more anemia and hypersensitivity/anaphylaxis reactions, and a higher incidence of mayor dermal and palmoplantar toxicity.

The regimen- and age-stratified multivariate analysis revealed lower dose reductions with Taxotere®, although only when the TC regimen was used. As regards anemia, the group of patients treated with the TC regimen showed Taxotere® to be associated with a lower risk than Hospira and Teva. In patients treated with the AC-T regimen, the risk was signifi-

Table 4. Cumulative incidence of adverse events associated with the different docetaxel products used in the study

	Docetaxel Actavis % (IC 95%)	Docetaxel Hospira % (IC 95%)	Docetaxel Accord % (IC 95%)	Taxotere® % (IC 95%)	Docetaxel Teva % (IC 95%)	*p*
Dose modification	17.0 (13.4-20.5)	8.3 (5.6-11.0)	26.0 (19.3-32.6)	7.1 (2.7-11.4)	18.8 (11.1-26.4)	< 0.001
Hospitalization	3.5 (1.7-5.3)	2.7 (1.1-4.3)	5.5 (1.9-9.1)	7.1 (2.7-11.4)	2.7 (0.6-7.6)	0.097
Emergency room visits	14.6 (11.2-17.9)	14.6 (11.2-18.0)	11.6 (6.7-16.5)	6.4 (2.2-10.6)	17.9 (10.3-25.4)	0.040
Anemia	40.7 (36.1-45.2)	31.5 (27.1-36.0)	38.1 (30.8-45.5)	7.1 (2.7-11.4)	33.9 (24.7-43.1)	< 0.001
Neutropenia	6.7 (4.3-9.1)	9.0 (6.2-11.8)	6.6 (2.7-10.5)	5.1 (1.3-8.9)	4.5 (1.5-10.1)	0.319
Febrile neutropenia	3.0 (1.4-4.7)	3.4 (1.6-5.2)	4.4 (1.1-7.7)	4.5 (0.9-8.1)	2.7 (0.6-7.6)	0.400
Hypersensitivity reactions-Anaphylaxis	7.6 (5.1-10.1)	2.0 (0.6-3.4)	6.1 (2.3-9.8)	3.2 (1.0-7.3)	0.0 (0.0-3.2)	< 0.001
Sensory neuropathy	18.0 (14.4-21.7)	18.5 (14.7-22.2)	4.4 (1.1-7.7)	18.6 (12.2-25.0)	18.8 (11.1-26.4)	< 0.001
Motor neuropathy	6.3 (4.0-8.6)	0.9 (0.2-2.3)	0.0 (0.0-2.0)	6.4 (2.2-10.6)	0.0 (0.0-3.2)	< 0.001
Palmoplantar toxicity	15.4 (12.0-18.8)	11.7 (8.6-11.8)	2.8 (0.9-6.3)	13.5 (7.8-19.1)	14.3 (7.4-21.2)	< 0.001
Dermatologic toxicity	34.1 (29.7-38.6)	16.2 (12.7-19.8)	19.9 (13.8-26.0)	18.6 (12.2-25.0)	25.0 (16.5-33.5)	< 0.001
Ungual toxicity	24.8 (20.7-28.8)	26.1 (21.9-30.3)	9.9 (5.3-14.6)	18.6 (12.2-25.0)	34.8 (25.6-44.1)	< 0.001
Facial edema	3.9 (2.0-5.8)	2.5 (0.9-4.0)	15.5 (9.9-21.0)	1.9 (0.4-5.5)	8.9 (3.2-14.7)	< 0.001
Limb edema	15.9 (12.4-19.3)	12.2 (9.0-15.3)	15.5 (9.9-21.0)	10.3 (5.2-15.3)	20.5 (12.6-28.5)	0.078

CI: confidence interval.

cantly lower with Taxotere® than with Actavis or Accord. Emergency room visits were observed to be much less frequent in patients on Taxotere® receiving a TC regimen. Patients on Taxotere®, however, showed a higher incidence of peripheral motor neuropathy than those on Actavis or Accord.

Discussion

Excipients commonly used in the different docetaxel products include polysorbate 80 and ethanol. Polysorbate 80 is a non-ionic surfactant whose main component is polyoxyethylenated sorbitan monooleate, which is structurally similar to polyethylene glycol (PEG). Experimental data indicate that polysorbate 80 can modify the drug's pharmacokinetic profile in a concentration-dependent manner and result in adverse events[9,10].

Polysorbate 80 is quickly degraded following intravenous administration, with dose increases revealing a linear pharmacokinetic profile. In vitro addition of polysorbate 80 to human plasma at clinically significant concentrations (> 5.0 µL/mL) results in an increase in unbound docetaxel (7% in the absence of polysorbate 80 vs 44% with polysorbate 80)[1]. Concentrations of unbound docetaxel are inversely proportional to those of alpha 1-acid glycoprotein (AAG) in plasma. As cancer patients exhibit great variability in their AAG levels, these differences may give rise to fluctuations in the pharmacokinetics of polysorbate 80 as well as in its activity and toxicity profile. Low levels of AAG have been associated with more severe neutropenia but with greater efficacy; lower levels tend to be related with lower efficacy[11]. Moreover, polysorbate 80 is not physiologically inert. Several studies have shown it to be a biologically and pharmacologically active compound that is often responsible for hypersensitivity reactions[12], peripheral neuropathy[12], and fluid retention/vascular toxicity[13,14]. Hypersensitivity reactions have been attributed in part to polysorbate 80's inherent toxicity[15], specifically to the oxidation of oleic acid and its derivatives, which give rise to the release of histamine. The role played by histamine in the etiology of infusional reactions is borne out by the fact that such reactions are minimized by premedication with corticoids and ntihistamines[8]. Apart from histamine, other vasoactive substances may play a role in hypersensitivity reactions to docetaxel[16]. In this study, it was not possible to ascertain that docetaxel's toxicity profile varied as a function of the amount of polysorbate 80 contained in the product.

As far as ethanol is concerned, cases of ethylic intoxication have been reported in patients receiving high doses of docetaxel or in pediatric patients, who tend to be more susceptible to the effects of alcohol. In 2014 the Food and Drug Administration issued a warning that administration of docetaxel could cause alcoholic intoxication following treatment. Some authors have correlated the dermal toxicity observed in some of these patients, probably of an irritative origin, with the administration of docetaxel products containing larger amounts of alcohol[7]. Our study found statistically significant differences regarding dermal toxicity in patients treated with docetaxel Actavis. Even if Actavis was the product containing the highest amount of ethanol in our study, the composition-related differences between the drugs analyzed here were not as marked as those reported in the previously mentioned study, where docetaxel formulations included far higher amounts of alcohol. This means that other factors could have also played a role in triggering the toxic reactions observed. As a result of this, this study was not able to determine which docetaxel product offered the safest toxicity profile.

As regards the amount of impurities contained in the different docetaxel products on the market, some studies indicate that generic formulations tend to cause more severe hematologic and skin toxicity and result in more discontinuations of treatment[17]. Some of those findings are comparable to the ones presented in this study, which identified a lower incidence of anemia and fewer dose reductions and visits to the emergency room with Taxotere®, the drug with the lowest content of impurities in the analysis. Nonetheless, these findings must be taken with caution as Hospira, which contains a higher amount of impurities, was the product in our study showing the lowest incidence of skin toxicity.

Significant differences were observed between the different docetaxel products analyzed in terms of their toxicity profile and clinical effect. These findings were in line with those described in another study of breast cancer patients treated with different docetaxel products, which also found different toxicity profiles for the different brands studied[18].

One of the main limitations of this analysis lies in its design as an observational study where two different regimens, with very different doses of the drug (one of them 33% higher than the other), were evaluated without properly balancing the different formulations. Although a multivariate analysis was carried out to minimize this bias, considering that the amount of docetaxel administered is the factor that most significantly influences toxicity, it would be advisable to carry out a specific study to compare the effect of excipients and impurities on both regimens separately. The other limitation was also related to the fact that the study was observational, as although it was prospective and multi-center, it included a reduced amount of patients from the different participating hospitals, which means that use of premedication and colony stimulating factors followed the practice of each of those centers, potentially leading to variations in the toxicity profile and clinical effect obtained.

In a nutshell, our study identified marked differences in the excipient and impurity concentrations of the studied docetaxel products. Differences were also found in the toxicity profile and clinical effect of the various products, some of them statistically significant. However, it was not possible to determine which of the products offered the best toxicity profile.

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Conflict of interest

No conflict of interest.

Contribution to the scientific literature

The development and introduction in the last few years of a large amount of different generic docetaxel formulations has made it possible to reduce the economic cost involved in treating different tumors.

There is contradictory data as to whether the fact that the different docetaxel products on the market contain varying amounts of excipients and impurities could influence the incidence of adverse events.

The study is a prospective observational analysis that compares the toxicity associated with different docetaxel products and analyzes whether the differences observed may be related with the amounts of excipients and impurities contained in each of them.

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