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Article

Adverse reactions to docetaxel: an active survey

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The rates of breast cancer mortality remain high in Brazil. Docetaxel is a semi-synthetic taxane used to treat various tumors, particularly tumors of the breast, lung and prostate. In this study ADR that occurred in 45 docetaxel users with breast cancer were surveyed. They were identified by type, causality (Naranjo algorithm and World Health Organization categories) and, if considered probable or defined, rated for severity according to SOBRAFO proposal (2007). A total of 325 ADR were observed: 165 in the first, 137 in the second and 23 in the third cycle. Fifty seven ADR were immediate and the others, late. Fatigue and exhaustion for more than five days, classified as Grade 3 by SOBRAFO (2007), were reported as the primary late RAM. There was no significant difference in the occurrence of immediate and late ADR between cycles (p=1 and p=0.3577, respectively). The presence of a pharmacist gave the patients a better understanding of the occurrence of RAM, especially those that occur outside the hospital, between chemotherapy cycles and are often not reported to the healthcare team, creating institutional demands and reaching the goal to track, observe and correlate the RAM for each user.

Uniterms: Docetaxel/adverse reactions. Drugs/adverse reactions. Breast Cancer/tretament/reactions.

As taxas de mortalidade por câncer de mama no Brasil permanecem altas. O docetaxel é um taxano semi-sintético usado para tratar vários tumores, particularmente tumores da mama, pulmão e próstata. Neste estudo, as Reações Adversas (RAM) ocorridas em 45 pacientes com câncer de mama foram monitoradas. Elas foram classificadas pelo tipo e causalidade (Algoritmo de Naranjo e categorias propostas pela Organização Mundial da Saúde) e, se consideradas prováveis ou definidas, foram classificadas também pela severidade, de acordo com a proposta da SOBRAFO (2007). Um total de 325 RAM foram observadas: 165 no primeiro, 137 no segundo e 23 no terceiro ciclo. Cinquenta e sete RAM foram imediatas e as demais tardias. Fadiga e exaustão por mais de 5 dias, classificadas como grau 3 pela SOBRAFO (2007), foram as principais RAM encontradas. Não houve diferença significativa na ocorrência de RAM imediatas ou tardias entre os ciclos (p=1 e p=0,3577, respectivamente). A presença de um farmacêutico proporcionou aos pacientes um melhor entendimento sobre a ocorrência de RAM, especialmente sobre aquelas que ocorrem fora do ambiente hospitalar, entre os ciclos da terapia, não sendo usualmente relatadas aos profissionais de saúde. Isto gerou uma demanda na instituição e permitiu alcançar a meta de acompanhar, observar e correlacionar as RAM de cada paciente.

Unitermos: Docetaxel/reações adversas. Medicamentos/reações adversas. Câncer de mama/tratamento/reações.

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INTRODUCTION

Although breast cancer has a relatively good prognosis, the rates of breast cancer mortality remain high in Brazil, most likely because the disease is still diagnosed in its advanced stages. According to the Ministry of Health, in 2012, 52,680 new cases of breast cancer were predicted, with an estimated risk of 52 cases per 100,000 women (INCA, 2011).

Docetaxel is a semi-synthetic taxane that is obtained from a precursor derived from the European tree Taxus baccata (Sweetman, 2008). It has been used to treat various tumors, particularly tumors of the breast (Bear *et al.*, 2003; Jones *et al.*, 2006), lung (Noble *et al*., 2006) and prostate (Kelly *et al.*, 2009). Its use can bring benefits such as increasing life expectancy and decreasing tumors, tumor progression and risk of relapse (Ghersi *et al.*, 2015). It is used as a first-line therapeutic treatment in combination with trastuzumab, a monoclonal antibody specific for HER2 receptor in metastatic breast cancers that express the HER2 receptor. As an adjuvant treatment of operable breast cancers that are lymph node positive, docetaxel can be administered with doxorubicin and cyclophosphamide (Sweetman, 2008). It can also be used alone, intravenously, as a neoadjuvant or as a palliative as a first, second or third choice, or in combination with cyclophosphamide every three weeks in adjuvant and neoadjuvant treatment (Brasil, 2006).

Adverse reactions to docetaxel have been reported for the gastrointestinal tract (ischemic colitis), heart (increased risk of heart failure), musculoskeletal system (arthralgia and myalgia), eyes (exacerbated tearing), skin and nails (foot-and-hand syndrome) and hypersensitivity reactions and tumor lysis syndrome (Sweetman, 2008). Cutaneous effects such as erythema (Tallon, Lamb, 2007) and onycholysis (Roh *et al.*, 2007) are responsible for the significant reduction in the quality of life of users. Undesirable hematological effects have been reported worldwide (Yip, Chow, 2006). The most important of these is febrile neutropenia, which is a dose-limiting factor because of its influence on the quality of life of users.

The Brazilian Society of Oncology Pharmacists (Sobrafo) has classified Adverse Drug Reactions (ADR) based on event severity. This classification system consists of five levels, where the lowest level (level 0) is defined as any adverse event or events within normal limits and the highest level (level 5) is death (Sobrafo, 2007). Table I shows examples of adverse reactions to docetaxel and their different degrees of severity as reported in the literature.

In this study, the adverse drug reactions observed in docetaxel users were surveyed, through an embryonic process of pharmaceutical care in a chemotherapy service. They were identified by type (infusion, immediate or late), categorized according to the Naranjo algorithm and World Health Organization categories and, for those considered probable or defined, rated for severity using the Sobrafo proposal (2007).

METHODS

The study was conducted in a small federal hospital that specializes in breast cancer care in Rio de Janeiro, Brazil. This unit is ambulatory and has 56 inpatient beds, a surgical center, and Radiotherapy and Chemotherapy units, but it lacks an Intensive Care Unit. The unit integrates the Sentinel Hospitals Program Hospital, a pharmacovigilance project of the Brazil Ministry of Health.

Pharmacovigilance is achieved through volunteer event reports that are sent to the Pharmacovigilance Department, without an active search for undesirable effects. Two recruitment processes were conducted. The first consisted of the first 20 patients selected for docetaxel therapy at the Oncology Clinic in December 2008, and the second consisted of the first 25 patients enrolled from August 2010 at the same clinic. The beginning of docetaxel therapy at this hospital occurs only after a health care team meeting. These meetings are held weekly to reach a consensus on the treatment being offered. The use of docetaxel is exclusive for patients who are elected at this meeting.

In the first group, patients were recruited from December 6 to 15, 2008, and follow-up occurred during the three weeks after each administration of docetaxel, with the last contact made on March 26, 2009. With the second group, the same strategy was applied: recruitment was held from August 18, 2009, to January 16, 2010. For this group, the last contact occurred on January 10, 2011.

The inclusion criteria were as follows: users aged 18 or older who used docetaxel in adjuvant protocols, neoadjuvant or palliative treatment during the two months from the date of this project approval and agreement to participate by signing the consent form. The exclusion criteria were the presence of communication difficulty or a lack of oral language comprehension by the user.

The sample size was established considering that the maximum number of simultaneous users of the drug in this hospital was 185 and that the lowest incidence of RAM to docetaxel reported in the literature was 10%. In addition, we selected an absolute precision of 10% and a confidence level of 95%. The minimum sample size of 10 patients was calculated by the software EPi INFO 7.1.4.0.

TABLE I - Example of RAM related to docetaxel, according to type and severity

RAM	Classification		Font
	Temporal	Severity	
Fatigue	Late	3 to 4	Engels, Verweij (2005)
Hives	Infusional/ Immediate	3	Limswuan, Demoly (2010)
Angioedema	Immediate	3	Limswuan,Demoly (2010); Raschi *et al.* (2010); Rodriguez-Frias, Lee (2007); Engels, Verweij (2005)
Anaphylaxis	Infusional /Immediate	3 to 4	Limswuan & Demoly (2010); Raschi *et al.* (2010)
Anaphylactic shock	Infusional/ Immediate	4 to 5	Limswuan, Demoly (2010)
Vasodilation	Late	3	Raschi *et al.*(2010)
Hypotension	Infusional/ Immediate	3	Raschi *et al.* (2010)
Syncope	Late	4 to 5	Raschi *et al.* (2010), Monsuez *et al.* (2010)
Phlebitis	Late	3	Raschi *et al*. (2010)
Liver damage	Late	3 to 4	Rodriguez-Frias, Lee (2007)
Peripheral Neuropathy	Late	3	Rodriguez-Frias, Lee (2007), Engels., Verweij (2005); Argyriou *et al.* (2008)
Neutropenia	Late	4	Rodriguez-Frias, Lee (2007); Engels, Verweij (2005)
Bradycardia	Immediate/ Late	3 to 4	Monsuez *et al.* (2010)
Arrhythmia	Late	3 to 5	Monsuez *et al.* (2010)
Myocardial Ischemia	Late	3 to 5	Monsuez *et al.* (2010)
Pericardial Effusion	Late	4 to 5	Monsuez *et al.* (2010)
Anemia	Late	3 to 5	Engels,Verweij (2005); Boneterre (1999)
Thrombocytopenia	Late	3 to 4	Engels, Verweij (2005); Boneterre (1999)
Febrile Neutropenia	Late	4 to 5	Engels, Verweij (2005); Boneterre (1999)
Náusea	Immediate/ Late	3 to 4	Engels, Verweij (2005)
Vomit	Immediate/ Late	3 to 4	Engels, Verweij (2005)
Diarrhea	Immediate/ Late	3 to 4	Engels, Verweij (2005)
Stomatitis	Late	3 to 4	Engels, Verweij (2005)
Erythrodysesthaesia palmar – plantar	Late	3 to 4	Kara, Sahin, Erkisi (2006)

After selection at the Clinical Meeting, patients scheduled the first docetaxel administration date at the chemotherapy center. According to this schedule, the pharmacist approached patients at this location, presenting the project and requesting their signature on the consent form. Only after this signature was obtained was Questionnaire 1 administered. This questionnaire concerned the patient's demographic data.

After drug administration, the patient returned to the Chemotherapy Center office to schedule their second medication cycle. The pharmacist was then informed of this date. On the appointed day, the pharmacist was once again with the patient during docetaxel administration and administered Questionnaire 2. This questionnaire, originally developed and validated to use in pregnant women by Canova (2005), was selected due to its simplicity and ease of understanding by the patient. It was previously validated to use with our patients, during a pilot test. The interview was held with the user and/or caregiver. This questionnaire was designed to capture information about the occurrence of late reactions (i.e., those that occur from three days after administration of the drug) during the period between treatments.

At least three weeks after the last administration,

the second questionnaire was administered again by telephone, so that data were collected for the period after the last drug administration. To prevent the interviewer from introducing bias, if the patient did not understand the question, it was read again. If necessary, a synonym to medical expressions was used like, for example, high blood pressure instead of hypertension. All patients underwent 3 cycles of docetaxel administration, with an interval of 23 days between them, unless the patient were to death.

In addition, we directly observed patients receiving docetaxel in the hospital to detect infusion reactions, which are those that occur at the time of drug administration. Patient records were also analyzed to search for additional information.

The causality of the suspect RAM was determined using the Naranjo Algorithm (Louro, Romano-Lieber, Ribeiro, 2007) and the cathegories proposed by the World Health Organization (WHO) (OPAS, 2011). To identify data in the literature concerning the event under suspicion, the following bibliographic databases were used: the product label, a reference book (Sweetman, 2008) and related articles (Roh *et al.*, 2007; Baker *et al.*, 2008). The temporal analysis of the adverse reactions was determined from direct observations of the drug administration, interviews and medical records. The appearance of the same RAM in two cycles of chemotherapy was considered recurrence of symptoms after re-exposure to the drug. It was not possible to measure the serum levels of the drug. However, the prescribed doses were checked against the literature. Alternative explanations of the symptoms were developed based on the literature and on discussions with the clinical staff accompanying the patient. Changes in dose (increase or decrease) were considered only when properly registered in the medical records. The use of drugs of the same family or with similar structure was considered for the analysis of item 9 of the Naranjo algorithm.

This work was recorded on July 22, 2008, under N° 075/08, and June 25, 2010, under N°. 073/10. The study was approved by INCA´s Ethics Committee on October 1, 2008, and August 13, 2010, and was in accordance with Resolution 196/96 of the National Council of Ethics in Human Research.

The data were stored and processed using Microsoft Excel®. We used descriptive statistics such as measures of frequency distribution, mean and standard deviation. To assess the statistical significance between differences in the occurrence of RAM in 3 cycles of chemotherapy with docetaxel, we used a 2 x 2 contingency table and Fisher´s exact test.

RESULTS AND DISCUSSION

Forty-five patients were followed. The sample contained only women, predominantly in the adjuvant treatment of breast cancer (51%), between 40 and 65 years old (82%), living in the metropolitan area of Rio de Janeiro State (82%), with 40% living in the capital itself. Most of the volunteers did not continue working during treatment (73%) and had less than 9 years of formal education (37%). The majority had at least one comorbidity (60 %), primarily hypertension, with a prevalence of 81.5%.

In this study, difficulty of access or symptom improvement were reported as reasons for non-admittance to the Hospital during an adverse event, regardless of the severity of RAM in all cases. This result confirms the observations of DI Girólamo (2000), who found that the distance between the Hospital and the residence of the volunteers was a factor for non-adherence to treatment. This observation reinforces the need for the pharmacist to use a closer approach to effectively observe any ADRs that occur between cycles of docetaxel administration.

Four volunteers did not complete the study. The causes were different in each case: death, change of antineoplastic treatment, protocol dropout and not understanding the study. Of those, three received two cycles of treatment, and one received only one dose. None of them reported RAM occurrence. The death was caused by the evolution of the disease, primarily lung and bone metastases. The antineoplastic protocol exchange took the appearance of brain metastases during treatment with docetaxel. In both cases, the volunteers were in palliative treatment. The case of non-adherence was due to social aspects: the volunteer had no means of transport and did not respond to queries because of her inability to pay transportation fees.

According to the analysis of causality made by the Naranjo Algorithm (Louro, Romano-Lieber, Ribeiro, 2007), all of the RAM were Probable. Applying the WHO categorization, 57,8% of the RAM were considered Defined, 42,1% were considered Probable and only one RAM was considered Possible. They were all were classified as late or immediate RAM. Immediate RAM begins three days after drug administration. Late RAM begins after the fourth day (OPAS, 2005). RAM severity was defined in accordance with the proposal of the Brazilian Society of Oncology Pharmacists (Sobrafo, 2007). Table II indicates the prevalence of each RAM and the severity rating. The occurrence of neutropenia and fatigue is worth noting.

It is important to note the higher incidence of immediate adverse reactions in the first cycle of treatment

TABLE II - Immediate and late RAM to docetaxel in different treatment cycles distributed according to the frequency of individuals (N) and degree of severity, N= 325, Rio de Janeiro, 2010

RAM	1st Cycle				2nd Cycle				3rd Cycle			
	Immediate		Late		Immediate		Late		Immediate		Late	
	N	Degree*	N	Degree*	N	Degree*	N	Degree*	N	Degree*	N	Degree*
Alopecia	-	-	-	-	-	-	-	-	-	-	1	1
Changes in the nails	-	-	-	-	-	-	-	-	1	2	2	2
Anxiety	-	-	1	2	-	-	-	-	-	-	-	-
Constipation	4	2	2	2	2	2	3	2	-	-	1	2
Diarrhea	2	2	11	2	-	-	10	2	1	2	9	2
Dyspnea	1	2	1	2	-	-	1	2	-	-	4	2
Headache	-	-	2	2	-	-	3	2	-	-	2	2
Backache	-	-	2	2	-	-	2	2	-	-	-	-
Leg pain	-	-	-	-	1	2	-	-	-	-	-	-
Pain in the abdomen	1	2	3	2	1	2	3	2	1	2	4	2
Pain in the body	3	2	6	2	-	-	5	2	-	-	8	2
Pain in the tumor	-	-	1	2	-	-	-	-	-	-	1	2
Pain in the limbs	-	-	6	2	-	-	14	2	-	-	8	2
Pain in the bones	1	2	3	2	1	2	3	2	1	2	4	2
Edema	-	-	2	2	-	-	2	2	-	-	2	2
Fatigue	4	3	20 3	3 4	4	3	18 4	3 4	1	3	15 4	3 4
Lack of appetite	-	-	5	1	-	-	-	-	-	-	4	2
Lack of taste	1	2	7	2	-	-	9	2	2	2	10	2
Insomnia	-	-	2	1	-	-	-	-	-	-	2	2
Mucosal irritation	1	2	6	2	1	2	6	2	-	-	7	2
Skin irritation	-	-	10	2	2	2	-	-	-	-	1	2
Eye irritation	-	-	2	1	-	-	1	2	-	-	1	1
Nausea	4	2	12	2	4	2	11	2	-	-	8	2
Febrile Neutropenia	-	-	6	4	-	-	2	4	-	-	2	4
Hot flushes	1	1	-	-	-	-	-	-	-	-	2	1
Paresthesia	1	2	2	2	-	-	2	2	1	2	5	2
Itch	-	-	9	2	-	-	3	2	-	-	5	2
Gastric Reflux	-	-	-	-	-	-	-	-	-	-	1	2
Flushing	2	1			1	2	-	-	-	-	-	-
Drooling	-	-	-	-	-	-	1	2	-	-	-	-
Syndrome foot-and-hand	1	2	-	-	-	-	-	-	-	-	2	2
Somnolence	-	-	2	1	-	-	1	2	-	-	-	-
Sweating	-	-	1	1	-	-	-	-	-	-	-	-
Tachycardia	-	-	2	2	-	-	3	2	-	-	2	2
Dry cough	-	-	1	1	-	-	1	2	-	-	1	2
Tremor	-	-	-	-	-	-	-	-	-	-	1	1
Vertigo	-	-	3	2	2	2	2	2	-	-	1	2
Blurred vision	-	-	1	2	2	2	-	-	-	-	-	-
Vomit	-	-	3	2			4	2	-	-	3	2
Xerostomia	-	-	1	3	1	3	1	3	-	-	-	-
Total RAM	27	-	138	-	22	-	115	-	8	-	15	-

*Severity was established in accordance with Sobrafo (2007)

compared with the second and third cycles, due to the initial drug exposure. As treatment continues, it is possible that the drug tolerance of the patient increases. It is noteworthy that the difference in the number of patients who showed immediate RAM among the three cycles was not statistically significant (p=0, 3577). There were more late reactions of more variety compared to the immediate reactions. For late reactions, there was no significant difference between cycles (p=1). Note that symptoms such as nausea, pain, fatigue, lack of taste, irritation (in skin or mucous membranes) and neutropenia occurred in all cycles in more than one patient. It is important to emphasize that there is a considerable reduction in the quality of life of patients with these symptoms, which is predictable and can be handled (Passareli, Jacob Filho, 2007).

Another feature to note is the recurrence of adverse reactions among users (Table III). Twenty-one ADR were reported in two cycles, and 11 RAM were reported in the three cycles. The symptoms discussed in the previous paragraph were cited as recurring in two and three cycles, thus reinforcing their importance.

Fatigue and exhaustion for more than five days, classified as Grade 3 by Sobrafo (2007), were reported as the primary late RAM for most volunteers. Both fatigue and prostration were classified as Probable. These two symptoms were described previously by Machado and Sawada (2008) as symptoms with increasing rates in the adjuvant treatment of breast cancer and bowel after three months of treatment. This adverse reaction, although treatable, is often overlooked in cancer treatment and can sometimes be confused with the evolution of the illness (Mota, Pimenta, 2002; Menezes, Camargo, 2006). We must be alert to the possibility of one symptom worsening another, as described by Lamino, Mota, Pimenta (2011). For example, fatigue can exacerbate the symptoms of pain, supporting the presence of a cluster of symptoms in breast cancer.

Another severe late RAM was febrile neutropenia, which was recurrent with thalassemia in one patient and non-recurring in eight other patients. This condition led to the hospitalization of the patients and was classified as grade 4. In such cases, a causal relation is likely. Febrile neutropenia is well known among the predictable RAM in breast cancer, and its management is widely reported (Gozzo *et al*., 2011).

Some RAM to docetaxel, such as facial flushing and hypertensive crisis upon infusion, may be related to comorbidities. In this study, all volunteers who had infusion reactions were hypertensive, and one patient who had recurrent febrile neutropenia was thalassemic. The literature (Brasil, 2006) suggests that infusion RAM are more common among patients in neoadjuvant treatments. However, our results show more adverse reactions among patients taking docetaxel as an adjuvant (Figure 1). It is noteworthy that 100% of the participants had late RAM, regardless of protocol type in at least one cycle of treatment, as highlighted in Figure 1. Hypersensitivity was reported by 8% of volunteers. It is noteworthy that no questions about the product quality were reported during the study period and that hypersensitivity reactions occurred with different batches of the product.

The presence of a pharmacist gave the patients a better understanding of the occurrence of RAM related to the use of docetaxel, especially those RAM that occur outside the hospital between chemotherapy cycles. These reactions are often not reported to the healthcare team. The contribution of the pharmacist at the Chemotherapy Center was exemplary and reflected the members of the

TABLE III - RAM to Docetaxel recurrence, N=45 patients, Rio de Janeiro, 2010

RAM	Recurrence	
	2 times	3 times
Constipation	4	0
Diarrhea	6	3
Headache	2	0
Backache	1	0
Pain in the limbs	7	2
Pain in the abdomen	2	1
Pain in the body	3	1
Pain in the bones	0	2
Edema	1	0
Fatigue	6	13
Lack of appetite	1	0
Lack of taste	4	3
Insomnia	1	0
Mucosal irritation	4	2
Skin irritation	3	0
Nausea	8	4
Febrile Neutropenia	1	0
Paresthesia	1	0
Itch	1	1
Tachycardia	0	1
Vertigo	1	0
Blurred vision	1	0
Vomit	1	0

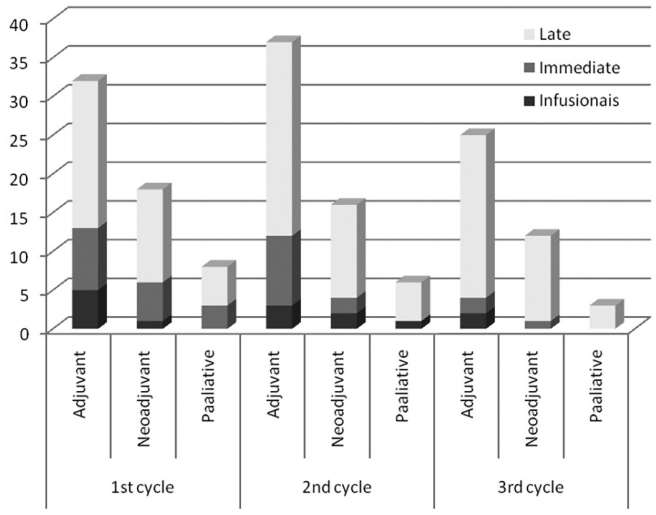

FIGURE 1 - Frequency of RAM in accordance with the treatment protocol and classification time of occurrence, N=325, Rio de Janeiro, 2010.

multidisciplinary team, creating institutional demands and reaching the goal to track, observe and correlate the RAM for each user. It is known that studies of this type reinforce the importance of pharmacovigilance and sensitize the entire multidisciplinary team. This sensitization may play a role in spontaneous ADR (Ribeiro-Vaz *et al*., 2011). The results, particularly the approach of the pharmacist to users of docetaxel, suggest that the implementation of an active pursuit of RAM in the intercycle period can be an important contribution of the Pharmacy Service in risk management, especially if this strategy can be expanded to other chemotherapy treatments offered by the institution.

Furthermore, as many late RAM ranged from moderate to severe, it is reasonable to suppose that they may therefore contribute to the impairment of treatment adherence or to a potential reduction in the patients' quality of life. Besides, these events, in more severe cases, may also increase the patients' risk of death.

The limited number of patients, the limited follow up period, the self report of the RAM and, consequently, the possibility of vies of memory, constitute the main limitations of this study. These limitations require caution in generalizing the results.

CONCLUSION

The objective of this work was an active search for adverse reactions to docetaxel among patients treated in a specialized breast cancer hospital in Rio de Janeiro. The results emphasize the necessity of monitoring adverse drug reactions during the inter cycle periods. The proposed methodology was adequate to the job, not only allowing the identification of the reactions of interest but also bringing the pharmacist closer to both the patients and the healthcare team.

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