

Comparing the Incidence of Febrile Neutropenia Resulting in Hospital Admission Between the Branded Docetaxel and the Generic Formulations

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Abstract

Studies have raised concern about the safety of generic compared with branded drugs. Febrile neutropenia (FN) resulting in hospital admission was compared between the branded docetaxel (Taxotere[®], Sanofi) and 2 generic formulations (docetaxel Ebewe and docetaxel Hospira) in patients with breast cancer. This was a retrospective study that included patients with breast cancer who received docetaxel between January 2012 and December 2014. Patients who had an admission diagnosis of FN and had received docetaxel within 14 days prior to admission were evaluated. The docetaxel brand and dose, patient characteristics, hospital length of stay, admission to the intensive care unit (ICU), and mortality were recorded. During the study period, 2904 cycles of docetaxel were given for 876 patients (1519 cycles of docetaxel Sanofi, 811 cycles of docetaxel Hospira, and 574 cycles of docetaxel Ebewe). Among the cycles given, 130 cycles were associated with FN that required hospital admission. The overall incidence of FN resulting in hospital admission was significantly higher in patients who had received docetaxel Hospira, compared with patients who had received docetaxel Sanofi (47[5.8%] cycles vs 53 [3.5%] cycles, $P = .009$), but there was no significant difference between docetaxel Ebewe and docetaxel Sanofi (30[5.2%] cycles vs 53 [3.5%] cycles, $P = .069$). All cases of FN resolved except for 1 patient who died in the ICU after receiving docetaxel Ebewe. There was a significant difference in the incidence of FN between docetaxel Sanofi and docetaxel Hospira, but all cases in both groups resolved completely.

Keywords

breast cancer, febrile neutropenia, docetaxel, generic, branded

Docetaxel is a chemotherapeutic agent that belongs to the taxane family and is approved for use in patients with breast cancer, non-small-cell lung cancer, prostate cancer, gastric cancer, and head and neck cancer.¹ The most common adverse reactions of docetaxel include neutropenia (84%), leukopenia (84%), alopecia (76%), weakness (66%), anemia (65%), fluid retention (60%), central nervous system toxicity (58%), stomatitis (53%), nail changes (41%), pulmonary reactions (41%), and fever (31%).^{1,2}

Febrile neutropenia (FN) is a serious side effect in patients with breast cancer receiving adjuvant chemotherapy that may lead to dose reductions or delay in the chemotherapy regimen.³ The incidence of chemotherapy-induced FN increases in the presence of risk factors such as older age, lower weight, higher dose of chemotherapy, higher number of chemotherapy cycles, lower baseline white blood cell count (WBC), lower neutrophil count, prior chemotherapy, and abnormal baseline liver or renal function.⁴

Docetaxel was originally manufactured by Sanofi-Aventis under the brand name Taxotere[®], and after it lost its patent protection, several generic products were produced. A generic drug is considered to be comparable to the original drug product in terms of quality,

performance, intended use, dosage form, strength, and route of administration.^{5,7} The main reason for using generic drugs is cost saving.⁸ The US Food and Drug Administration (FDA) approves generics of branded medications based on a number of criteria including bioequivalence.⁹

The safety pattern of the generic formulations has been the subject of debate. Studies have reported differences between the original drugs and the generics in terms of active ingredients and impurities.^{6,7,10,11} It has been reported that 90% of generic docetaxel formulations contain an insufficient amount of active drug, high levels of impurities, or both, which may affect both efficacy and safety.⁶

This study was triggered by a case of fatal FN following docetaxel treatment. The incidence occurred after a switch from the branded docetaxel to the

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generic formulations at the institution. Little is known about the difference in the incidence of FN between the branded docetaxel and the generic formulations available.^{5,12} The objective of this study was to assess the incidence of FN resulting in hospital admission in patients with breast cancer after receiving the original docetaxel (Taxotere[®], Sanofi) or a generic formulation (docetaxel Hospira or docetaxel Ebewe) in patients with breast cancer.

Methods and Patients

This was a retrospective study conducted at King Hussein Cancer Center (KHCC), a 170-bed comprehensive cancer center in Amman, Jordan. The study was approved by the institutional human subjects review board with a waiver of consent for retrospective, deidentified data collection and analysis.

Patients with breast cancer who had received docetaxel between January 2012 and December 2014 were identified using the electronic databases of the medical records and the pharmacy. Patients typically receive docetaxel at the chemotherapy outpatient clinics at KHCC, which serve an average of 1800 patients per month. Patients with locally advanced and metastatic breast cancer were enrolled. Among the patients identified, we evaluated patients who had a hospital admission diagnosis of FN and had received docetaxel within 14 days prior to admission.

For patients who were admitted to the hospital with a diagnosis of FN within 14 days of receiving docetaxel, the patient characteristics, stage of cancer, previous chemotherapy regimens, hospital length of stay (LOS), admission to the intensive care unit (ICU), and mortality were identified. In addition, we recorded the docetaxel dose, source, the supportive therapy given, the results of the cultures taken at the time of admission as well as the liver function tests and albumin levels on the day of docetaxel administration and on the day of hospital admission.

FN resulting in hospital admission associated with the administration of the 3 different formulations of docetaxel including docetaxel Sanofi (Taxotere[®]), docetaxel Hospira, and docetaxel Ebewe was evaluated, and a comparison between the incidences of FN with the original docetaxel Sanofi was done.

Statistical Analysis

Continuous data were presented as mean and SD, and nominal data were presented as absolute numbers and percentages. The incidence of FN, which was the primary endpoint for the study, was compared among the branded and each of the generic formulations using Chi-squared tests. A *P* value < .05 was considered significant. It was estimated that 321 cycles per group

were required to find a 5% difference in the primary endpoint with 90% power.

A subgroup analysis was conducted to assess the impact of the docetaxel dose on the incidence of FN. The incidence of FN was compared between the branded docetaxel 100 mg/m² and each of the generic formulations at the 100 mg/m² dose. In addition, a similar comparison was conducted for the docetaxel 75 mg/m². All analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

During the study period, 2904 cycles of docetaxel were given to 876 patients (1519 cycles of docetaxel Sanofi, 811 cycles of docetaxel Hospira, and 574 cycles of docetaxel Ebewe). Among the cycles given, 130 cycles (4.5%) were associated with admission to the inpatient medical oncology service at KHCC for the management of FN. In the majority of these cases, FN resulting in hospital admission occurred after the first cycle of docetaxel (67%). The remaining cases occurred after 2 or more cycles. Among the cases who were admitted with FN, 7 cases (5.3%) had received filgrastim as prophylaxis after receiving docetaxel, and 6 cases (4.6%) had elevated baseline liver enzymes at the time of receiving docetaxel. Three cases of elevated baseline liver enzymes were treated with docetaxel Hospira, and the other 3 received docetaxel Sanofi. The mean albumin level on the day of docetaxel administration was 4.1 ± 0.4 (SD), and the mean albumin level on the day of admission was 3.8 ± 0.4 (SD). The absolute neutrophil count (ANC) on the day of admission for the majority of the patients was less than 500 except for 3 cases that were between 500 and 1000. All patients had a baseline ANC above 1000 before starting docetaxel. Among the 130 cases of FN, 18 (13.8%) cases had documented infection (ie, positive cultures), and the remaining patients had cultures that were negative. The characteristics and outcomes of patients who developed FN resulting in hospital admission receiving the branded docetaxel and the 2 generic formulations are outlined in Table 1.

The overall incidence of FN resulting in hospital admission was significantly higher in patients who had received docetaxel Hospira prior to admission, compared with patients who had received docetaxel Sanofi (47[5.8%] cycles vs 53 [3.5%] cycles, *P* = .009), but there was no significant difference between docetaxel Ebewe and docetaxel Sanofi (30 [5.2%] cycles vs. 53 [3.5%] cycles, *P* = .069).

During the study period, a total of 533 patients (1559 cycles) received docetaxel at a dose of 100 mg/m² (805 cycles of docetaxel Sanofi, 421 cycles of docetaxel

Table 1. Patient Characteristics for Patients Who Received the Original and the Generic Formulations of Docetaxel

	Ebewe N = 30	Hospira N = 47	Sanofi N = 53
Age, mean (SD)	52.5 (11.78)	52.4 (11.55)	52.79 (11.8)
Sex; Female, n (%)	30 (100%)	47(100%)	53 (100%)
Stage of breast cancer, n (%)			
Locally advanced breast cancer	22 (73.3%)	37 (78.7%)	39 (73.6%)
Metastatic breast cancer	8 (26.7%)	10 (21.3%)	14 (26.4%)
Previous chemotherapy regimens prior to docetaxel, n (%)			
AC ^a	19 (63.3%)	16 (34%)	33 (62.3%)
FEC ^b	8 (26.7%)	23(49%)	13 (24.5%)
Others	0	1 (2.1%)	2 (3.7%)
No chemotherapy	0	4 (8.5%)	2 (3.7%)
Hormonal therapy	3 (10%)	3 (6.4%)	3 (5.7%)
Absolute neutrophil count at hospital admission, mean (SD)	146 (136.5)	146 (137.6)	148.7 (139)
Docetaxel cycle associated with admission due to FN			
Cycle 1, n (%)	22 (73.3%)	29 (61.7%)	36 (68%)
Cycle 2, n (%)	4 (13.3%)	13 (27.7%)	5 (9.4%)
Cycle 3 or more, n (%)	4 (13.3%)	5 (10.6%)	12 (22.6%)
Patients received docetaxel 100 mg/m ² , n (%)	22 (6.6%)	35 (8.3%)	36 (4.5%)
Patients received docetaxel 75 mg/m ² , n (%)	8 (3.3%)	12 (3.1%)	17 (2.5%)
Baseline albumin level, mean (SD)	4 (0.4)	4.1 (0.3)	4.1 (0.4)
Cases received filgrastim following docetaxel administration, n (%)	1 (3.3%)	3 (6.4%)	3 (5.7%)
Hospital length of stay, mean days (SD)	4.18 (2.16)	4.2 (2.15)	4.18 (2.14)
Intensive care unit admission, mean (SD)	1 (3.3%)	1 (2.12%)	1 (1.9%)
Mortality, n (%)	1 (3.3%)	0	0

^aAC: doxorubicin and cyclophosphamide.

^bFEC: 5-fluorouracil, epirubicin, cyclophosphamide.

Hospira, and 333 cycles of docetaxel Ebewe), while 343 patients (1345 cycles) received docetaxel at a dose of 75 mg/m² docetaxel (714 cycles of docetaxel Sanofi, 390 cycles of docetaxel Hospira, and 241 cycles of docetaxel Ebewe). Among cases who were admitted with FN, 98 patients had received docetaxel at a dose of 100 mg/m² vs 32 patients who had received docetaxel at a dose of 75 mg/m². In a subgroup analysis based on the docetaxel dose administered, the incidence of FN was significantly higher in patients who had received docetaxel Hospira 100 mg/m² compared with patients who had received docetaxel Sanofi 100 mg/m² (8.3% vs 4.5%, $P = .006$). There was no significant difference in the incidence of FN between the 2 groups in patients who had received a dose of 75 mg/m² for both products (Hospira 3.1% vs Sanofi 2.4%, $P = .489$). In addition, there was no significant difference between patients who had received docetaxel Ebewe and docetaxel Sanofi at the 100 mg/m² dosing regimen (Ebewe 6.6% vs Sanofi 4.5%, $P = .136$) or at the 75 mg/m² dosing regimen (Ebewe 3.3% vs Sanofi 2.4%, $P = .430$).

Among cases of FN, 127 cases (97.7%) resolved and were discharged home after a mean of 4.2 days $\pm$ 2.1 (SD), while the remaining 3 patients were transferred to the ICU; 1 patient who received docetaxel Ebewe died. This patient had locally advanced disease for which she had received 4 cycles of AC prior to docetaxel and 1 cycle of docetaxel that resulted in admission for FN.

Discussion

Generic formulations are widely used to reduce health care cost.^{6,13} Equivalence and bioequivalence with the originator drug are a requirement for licensing of the generic product. Being identical in the active ingredient, strength, dosage, route of administration, and therapeutic indication is required for a drug to be approved in equivalence studies. However, differences in the inactive ingredients and product characteristics are permitted.⁵ Differences in generic formulations arise not only from the differences in the amount of active ingredients present but also the presence and quantity of excipients, which may modulate the quality of generic formulations. Global assessment regarding the quality of different docetaxel formulations should be taken into account in terms of the amount of excipients or the presence of certain unapproved excipients.⁶

In this study, FN that resulted in hospital admission was compared between the original brand and 2 generic formulations of docetaxel (Ebewe and Hospira) in a comprehensive cancer center, and subgroup analysis based on the dose of docetaxel was done. The difference in the toxicity profile between different doses of docetaxel was previously addressed in a phase 3 trial, which demonstrated an increase in the incidence of FN when the doses were increased.¹⁴

To our knowledge, few studies evaluated the difference between the original docetaxel and the generic formulations in terms of side effects.^{5,6,12,15} Differences in adverse reactions between the branded chemotherapeutic agents and their generic products were previously addressed.^{16–18} One study was conducted to evaluate the pharmaceutical quality of 31 commercially available generic formulations of docetaxel by comparing their docetaxel content and impurity levels vs those for docetaxel Sanofi. The study concluded that 90% of the generic docetaxel formulations contained insufficient active ingredients and/or high levels of impurities, which may affect both the efficacy and safety of the drug.⁶

In another study, the incidence of acute infusion reactions (grade ≥ 3) and clinically significant skin reactions were compared among 4 different formulations of docetaxel, including the original drug. The study reported that acute infusion reactions of docetaxel may be due to the presence of certain excipients used in different formulations.¹⁵ The 3 products of docetaxel used in our study contained ethanol and polysorbate 80.^{1,19,20} The ethanol content in docetaxel products may affect the central nervous system and cause symptoms of intoxication.¹ The presence of polysorbate 80 in docetaxel formulations has been associated with hypersensitivity reactions.²¹ However, none of the 3 products contained excipients that are known to be associated with infection or fever.

In mid-2010, Sanofi-Aventis changed the formulation of docetaxel. The only difference between the 2 formulations was the quantity of ethanol. This change was evaluated in a retrospective study in breast cancer patients treated in adjuvant and neoadjuvant settings. The study showed a significant increase in the incidence of cutaneous toxicity and neurologic side effects following the change in formulation, which was reported by the French health authorities. This increase could be attributed to the higher doses of docetaxel used and the increase in ethanol content in the new formulation.²²

A study evaluated docetaxel side effects in a tertiary breast cancer center by comparing the occurrence of grade III and IV side effects including FN, hand foot syndrome, thrombotic events, intestinal perforation, and death between the original docetaxel Sanofi and the generic formulation docetaxel Hospira.⁵ Patients who received both formulations during the study period were excluded. The doses of docetaxel ranged between 75 mg/m² and 100 mg/m², which was the same dosage range used in our study. The study reported a comparable number of side effects with docetaxel Hospira compared with docetaxel Sanofi, but grade IV FN was more frequent in patients receiving docetaxel Hospira.⁵ The study showed a higher rate of treatment discontinuation despite increasing the use of filgrastim

in the generic group, which may impact outcomes, especially in the adjuvant treatment.⁵

Docetaxel is more than 90% protein bound.²³ Studies have shown that exposure to unbound docetaxel is related to hematologic side effects including neutropenia.^{23–25} In our study the albumin level was within normal range, as the majority of patients had local disease and were not heavily pretreated with multiple lines of chemotherapy.

The main reason to use generic drugs is to reduce the cost; however, if the generic drugs caused more adverse events that resulted in hospital admission, the benefit of cost saving might be lost. In our study the incidence of FN that resulted in admission was significantly higher using the generic drug (docetaxel Hospira) compared with the branded docetaxel. For patients who received docetaxel Hospira, the number needed to harm (NNH) was 43 (ie, for each 43 patients treated with docetaxel Hospira, 1 additional patient may develop FN that requires hospital admission). For the subgroup that received docetaxel Hospira 100 mg/m², the NNH was 26. Although the FN had resolved in all patients who received docetaxel Hospira, the clinical significance of the finding would be related to the direct and indirect cost of hospital admission.

The present study has a few limitations. First is the retrospective nature of the study, which would carry with it the limitations of retrospective studies. However, all data were collected from the electronic databases to minimize the potential for documentation errors. In addition, we did not assess the underlying comorbidities or the drug-drug interactions between docetaxel and other medications in patients who developed FN, and we did not have a method to objectively assess the diagnosis of FN or to assess its severity upon admission. Identifying drug history at the time of docetaxel administration was not feasible. However, this study is the first to provide a comprehensive comparison between the original docetaxel brand and 2 of the generic formulations in terms of the incidence of FN resulting in hospital admission. The findings of the study may help in decision making based on the expected cost saving associated with the generic products and the predicted expenditure required for managing the additional complications and adverse events.

Conclusion

The incidence of FN was higher in patients who received the generic formulation (docetaxel Hospira) compared with the branded docetaxel. Although most of the cases of FN resolved, this area needs to be further studied to determine the clinical significance of that difference.

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