DOCETAXEL-INDUCED FEBRILE NEUTROPENIA IN BREAST CANCER PATIENTS IN MALAYSIA

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Abstract

Docetaxel induced febrile neutropenia (FN) is a common adverse event encountered by breast cancer patients worldwide, especially among Asian patients. We aim to evaluate incidence of FN in breast cancer patients receiving docetaxel in Malaysia.

We retrospectively reviewed the records from patients with breast cancer who received docetaxel in a university-hospital. The incidence of FN, length of hospital stay, incidence of ICU admission, incidence and grade of neutropenia were evaluated.

Among 237 breast cancer patients, incidence of FN was 14.34% (34 patients). Mean length of hospital stay was 9.28 days (2 to 94 days). Two patients (0.84%) required admission to the ICU with the length of stay being 4 and 60 days respectively. Incidences of neutropenia are 27.8% (grade 1), 0.8% (grade 2), 1.69% (grade 3) and 0.4% (grade 4).

The incidence of febrile neutropenia due to docetaxel was higher among this population. This data may help to determine the optimal dose of docetaxel in breast cancer patients.

Keywords: Breast cancer, Chemotherapy, Docetaxel, Febrile neutropenia

Introduction

Breast cancer is the most prevalent cancer among women in Malaysia, accounting for 32.1% among all cancers in women (1).

Docetaxel is used in the neoadjuvant, adjuvant and palliative settings in breast cancer. Docetaxel is a taxane derivative similar to paclitaxel. It is derived from extracts of the leaves of European yew tree (Taxus baccata) (2). Docetaxel binds to tubulin, the protein component of microtubules, and simultaneously promotes assembly and inhibits disassembly of them (2). Stabilization of microtubules leads to inhibition of mitosis and tumour proliferation, resulting in cell death (2).

Febrile neutropenia is a significant morbidity for patients undergoing chemotherapy. Overall, febrile neutropenia rate due to docetaxel is in the range of 11-25% (3). In general, there seems to be a trend of higher febrile neutropenia rate among Asian patients regardless of the type of chemotherapy (4). CLEOPATRA study is a landmark paper that investigated combination of trastuzumab with docetaxel with or without pertuzumab for HER2 positive metastatic breast cancer (5). A subgroup analysis of Asian and non-Asian subjects in the CLEOPATRA study showed 18.6% of febrile neutropenia in Asian group compared to 7.1% in the non-Asian group (5). A pharmacokinetic and pharmacodynamic study conducted in Singapore found that docetaxel clearance was about 30% lower while drug exposure (area under the curve) was about 25% higher in Asians compared to reported data in Caucasians (6).

According to the Malaysia Ministry of Health systemic therapy of cancer guideline, the recommended starting dose for docetaxel is 75 – 100 mg/m^2 every 3 weeks in the neoadjuvant and adjuvant setting; 75 to 100 mg/m^2 every 3 weeks or 35 mg/m^2 on day-1, day-8 and day-15 every 28 days in the palliative setting (7).

In our centre, the common starting dose is 75 – 90 mg / m^2 every 3 weeks as part of a sequential anthracycline-taxane regimen (3 cycles of 5-fluorouracil, epirubicin, cyclophosphamide followed by 3 cycles of docetaxel) in the neoadjuvant or adjuvant setting. As for palliative setting, the common starting dose is 60 – 75 mg/m^2 as single agent. Prophylactic G-CSF (granulocyte colony stimulating factor) is not widely used for patients with breast cancer in Malaysia due to the high cost of therapy to the hospital.

To date, there are no published Malaysian data on the febrile neutropenia rate due to docetaxel among breast

cancer patients. This study will contribute to the deeper understanding of the rate and implications of febrile neutropenia due to docetaxel in the Malaysian population.

Methods

We retrospectively reviewed the electronic medical records for patients diagnosed with early or metastatic breast cancer from January 2013 to December 2017 in a university-hospital oncology day care unit. Inclusion criteria include histologically confirmed breast invasive carcinoma; patients who received at least one dose of docetaxel as single agent or as part of a sequential treatment. Patients who received docetaxel in combination with another chemotherapy drug or HER-2 targeted agents were excluded.

The incidence of febrile neutropenia, incidence and length of hospital stays, incidence of intensive care unit (ICU) admission, incidence and grade of neutropenia were evaluated.

Medical records for all patients were reviewed including discharge summaries from regional hospitals to evaluate the incidence and severity of febrile neutropenia. Febrile neutropenia is defined by an absolute neutrophil count (ANC) less than 1000/mm^3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of $\geq$ 38 degrees C (100.4 degrees F) for more than one hour. Standard of care is that no routine granulocyte-colony stimulating factor was given as primary prophylaxis; however, it is permitted for secondary prophylaxis for patients with history of febrile neutropenia. All patients were instructed to visit the emergency department if they developed fever above 38 degrees C. If confirmed to have febrile neutropenia, they were admitted and managed as per institutional guideline.

Complete blood count was performed on the day of planned chemotherapy prior to reconstitution of docetaxel. Neutropenia is graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 defined as ANC between 1500/mm^3 to lower limit of normal; grade 2 defined as ANC between 1000 to 1500/mm^3; grade 3 defined as ANC between 500 to 1500/mm^3; and grade 4 defined as ANC below 500/mm^3.

This study was approved by the Universiti Kebangsaan Malaysia research and ethics committee.

Results

We identified in total 237 breast cancer patients who received at least 1 dose of docetaxel. The baseline characteristics are outlined in Table 1. Most of these patients received docetaxel in the adjuvant setting (65.8 %), followed by 20.5% in the palliative setting and 13.5% in the neoadjuvant setting. All of these patients received docetaxel at 3-weekly interval, as sequential with an anthracycline based chemotherapy or as single agent. None of the patients received dose-dense chemotherapy.

Table 1: Baseline characteristics

Characteristics	No (%)
Age, years	
Range	21 - 70
Median	52
Sex	
Male	1 (0.4)
Female	236 (99.6)
Race	
Malay	143 (60.3)
Chinese	68 (28.7)
Indian	19 (8.0)
Others	7 (3.0)
Treatment intent	
Adjuvant	156 (65.8)
Neoadjuvant	32 (13.5)
Palliative	49 (20.7)
Single agent/sequential treatment	
Docetaxel-only	47 (19.8)
Sequential anthracycline-docetaxel	190 (80.2)

The overall incidence of febrile neutropenia was 14.34% (34 patients) as shown in Figure 1. The highest FN rate was observed in the palliative setting at 16.3%, followed by 14.1% in the adjuvant setting and 12.5% in the neoadjuvant setting. As for asymptomatic neutropenia, the overall incidence was 30.8% with majority of cases being grade one or two according to CTCAE (Figure 2). Similar to the FN rate, asymptomatic neutropenia was most commonly observed in the palliative setting at 36.7%, followed by 31.3% in the neoadjuvant setting and 28.8% in the adjuvant setting.

The mean length of hospital stay due to febrile neutropenia was 9.28 days (ranged 2 to 94 days). Two patients (0.84%) required admission to the intensive care unit with the length of stay being 4 and 60 days respectively. Incidences of neutropenia are 27.8% (grade 1), 0.8% (grade 2), 1.69% (grade 3) and 0.4% (grade 4). Among 38 episodes of hospital admission for febrile neutropenia, there were 3 admissions longer than 10 days i.e. 19, 31 and 94 days. There was no mortality reported.

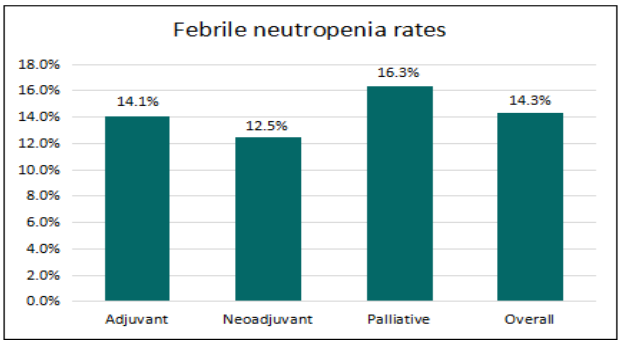

Figure 1: Graph shows febrile neutropenia rates in association to treatment intent

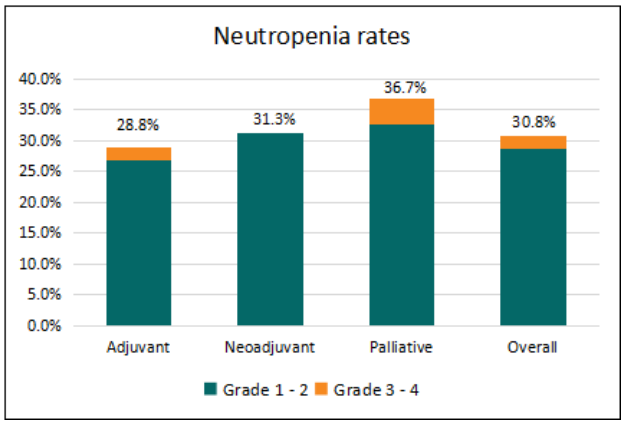

Figure 2: Graph shows neutropenia rate and grade in association to treatment intent

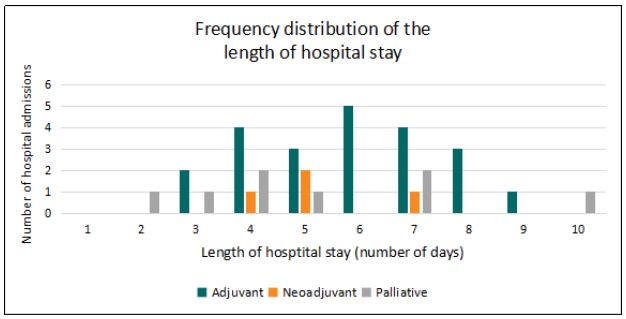

Figure 3: Graph shows frequency distribution of length of hospital stays

Discussion

Docetaxel is generally a well-tolerated chemotherapy. Febrile neutropenia is a recognized adverse event that may be serious and life-threatening. Most publications on febrile neutropenia rates involved non-Asian patients in clinical trial setting. It is important to provide febrile neutropenia rates derived from Asian patients from daily clinical practice to derive useful local recommendations. This study is a single centre, retrospective study that evaluated the incidence of febrile neutropenia secondary to docetaxel among breast cancer patients.

In this study, 14.3% of patients had at least 1 episode of febrile neutropenia. This is remarkably higher than the reported febrile neutropenia rate in various landmark clinical trial summarised below, more so in comparison to the Caucasian population. This is despite the lower starting dose of docetaxel in the Malaysian setting. There was no use of granulocyte colony-stimulating-factor (G-CSF) as primary prophylaxis in this study, as per the local institutional guideline. G-CSF is permissible as secondary prophylaxis for patients with history of febrile neutropenia. It is worth noting that most oncologists would reduce the dose of docetaxel after an episode of febrile neutropenia.

Table 2: Summary of febrile neutropenia and neutropenia rates in various landmark breast cancer studies in comparison to this study

Study	Population	Treatment regimen	Febrile neutropenia rate	Neutropenia rate
Roche et al (8)	Caucasian	FEC x 3, T x 3	7.9%	10.9%
Chow et al (9)	Caucasian Asian	TC x 4 TC x 4	9% 15%	6% 45.7%
Lee et al	Asian	FEC x 3, T x3 (adjuvant) FEC x 3, T x 3 (neoadjuvant) T x 6 Any Docetaxel containing regimen	14.1% 12.5% 16.3% 14.3%	28.8% 31.3% 36.7% 30.8%

FEC: 5Fluorouracil/Epirubicin/Cyclophosphamide; T: Docetaxel; TC: Docetaxel/Cyclophosphamide.

In our centre, all patients with febrile neutropenia mandate hospital admissions and treatment with isolation, broad spectrum antibiotics e.g., piperacillin-tazobactam or cefepime, and subcutaneous granulocyte colony-stimulating-factor. There were 38 episodes of hospital admission for febrile neutropenia recorded, with mean stay of 9.28 days, as well as 2 intensive care unit (ICU) admissions. Management of febrile neutropenia varies between centers and countries depending on the socioeconomic status, patient selection for chemotherapy, accessibility of health care facilities etc. The endpoints of hospital admissions and ICU admissions are not commonly reported and compared in most studies. However, it is evident that oncologists aim to reduce morbidity and mortality due to chemotherapy, to improve treatment outcomes.

This study has a few limitations. This was a retrospective study with no standardization of docetaxel dosage. The nature of this study is also subjected to recall bias and incomplete data. Retrospectively, we think that collection of the exact docetaxel doses could have been useful to analyse the association between dosing and incidence of febrile neutropenia. Overall, we believe that our data remains relevant and address the scarcity of Asian data.

Conclusion

The understanding of the febrile neutropenia rate in local context may help to determine the optimal dose of docetaxel and treatment strategies to prevent febrile neutropenia. The risk-benefit ratio is key in determining the optimum chemotherapy.

Acknowledgements

We would like to acknowledge the Universiti Kebangssan Malaysia Medical Center oncology day care unit for the assistance in data collection.

Author Contributions

DL and FI conceived and designed the study. DL conducted the data collection and statistical analysis. DL and FI wrote the article.

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Data Availability Statements

The data that support the findings of this study are available upon requests from the authors.

Competing interests

Both authors declare none.

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