ORIGINAL ARTICLE

Two-weekly docetaxel in treatment of advanced breast cancer: A preliminary study

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ABSTRACT

Objective: Three-weekly docetaxel causes a high rate of febrile neutropenia, especially in the Asian population. Two-weekly docetaxel has been shown to reduce rate of febrile neutropenia in castrate-resistant prostate cancer patients. We conducted a preliminary study to investigate the safety of two-weekly docetaxel in advanced breast cancer patients. Methods: We recruited 10 patients with advanced breast cancer with ECOG (Eastern Cooperative Oncology Group) performance status score of zero to two, who needed chemotherapy in the first or second-line setting to receive two-weekly docetaxel for 8 cycles. The primary endpoint was safety and secondary endpoints were response rate and progression free survival.

Results: The most reported adverse events were haematological (anaemia 100% and neutropenia 90%). The febrile neutropenia rate was 10%. The overall response rate was 20%. The median progression free survival was 5.0 months.

Conclusion: Two-weekly docetaxel may be a reasonable alternative treatment regimen for patients with advanced breast cancer in the first or second-line setting. This regimen is yet to be compared with standard 3-weekly schedule in a phase 3 randomised clinical trial.

KEY WORDS:

Advanced breast cancer, Chemotherapy, Docetaxel, Taxane

INTRODUCTION

Breast cancer is the most prevalent cancer among women in Malaysia, accounting for 32.1% among all cancers in women.[1] Docetaxel as a single agent is one of the treatment options in advanced breast cancer. Docetaxel is a taxane derivative similar to paclitaxel. It is derived from extracts of the leaves of European yew tree (Taxus baccata). Docetaxel acts by binding to tubulin, the protein component of microtubules, and simultaneously promotes assembly and inhibits disassembly of them. Stabilisation of microtubules leads to inhibition of mitosis and tumour proliferation, resulting in cell death.

Docetaxel was first approved for use by the US Food and Drug Administration (FDA) in 1996 for locally advanced or metastatic breast cancer after failure of prior chemotherapy, with a dose of 60 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.[2] In Caucasians, the common starting dose is 100mg/m^2. However, in the Asian setting, the common starting dose is 70 to 75mg/m^2. In Japan the approved starting dose is 60mg/m^2.[3] Despite the discrepancy in dose, the incidence of febrile neutropenia is higher in Asian patients.[4] In the CLEOPATRA trial investigating combination of pertuzumab, trastuzumab and docetaxel for HER2 positive advanced breast cancer, docetaxel dose reductions below 75 mg/m^2 occurred in 47% of patients from Asia compared with 13% of patients from other regions.[5] However, the dose reductions did not adversely affect the efficacy of docetaxel. An analysis comparing the Asian and non-Asian subjects in the CLEOPATRA trial showed higher incidence of adverse events in Asian women e.g. febrile neutropenia (18.6% vs. 7.1%), myalgia (42.3% vs. 14.7%) and upper respiratory tract infection (25.7% vs. 10.2%).[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.[4]

In our clinical practice, patients often require dose reduction of docetaxel due to intolerability to adverse events. As the risk of febrile neutropenia is high, especially in patient with poor performance status and advanced cancers, the usual starting dose is 60-80 mg/m^2. We retrospectively reviewed breast cancer patients who received docetaxel in our centre from 2013 to 2017 and showed 30.8% of neutropenia rate and 14.3% of febrile neutropenia rate among breast cancer patients either in the neoadjuvant, adjuvant or palliative setting.[6]

Three phase 2 studies concluded that the use of weekly 35-40 mg/m^2 docetaxel, on a schedule of weekly treatment for 6 weeks and followed by a 2-week break produces response rates ranging from 33 to 50% in patients with advanced breast cancer which is similar to the 3 weekly regime.[7-10] They also reported lower incidence of myelosuppression. However, weekly docetaxel may not be a popular option due to increased hospital visits and costs of treatment.

A phase 3 randomised clinical trial comparing 2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate

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cancer showed 50mg/m² docetaxel administered every 2 weeks was well tolerated and improved time to treatment failure and median overall survival.[11] The rate of febrile neutropenia was 14% in the 3-weekly docetaxel group and 4% in the 2-weekly docetaxel group. However, this 2-weekly regime has not been studied in ABC. Currently there is a randomised clinical trial in China comparing 2-weekly versus 3-weekly docetaxel in HER2 negative metastatic breast cancer. This trial is still in the recruitment phase.[12]

In advanced cancer setting where the goal is palliation, avoiding risks of major toxicities such as sepsis, and at the same time reducing inconvenience of repeated visits which maintaining efficacy are all important goals. It is important to determine the optimal dose and interval of docetaxel for Malaysian patients in routine clinical settings. Two regimens of docetaxel are listed in the Malaysia Ministry of Health systemic therapy of cancer protocol including docetaxel 75 to 100mg/m^2 every 3 weeks or docetaxel 35mg/m^2 on day-1, day-8 and day-15 of a 28-days cycle.[13] We are proposing a 2-weekly chemotherapy schedule to try optimize balance of efficacy, risk and convenience to patients with advanced breast cancers.

MATERIALS AND METHODS

Patients

We screened and treated 10 patients in the University Kebangsaan Malaysia Medical Centre between 1st November 2017 and 30th August 2018. Eligible patients had locally recurrent, unresectable, or metastatic breast cancer. Diagnosis of breast cancer were histology confirmed. Patients must have measurable disease. Additional eligibility criteria were: an age of 18 years to 75 years, Eastern Cooperative Oncology Group (ECOG) performance status of zero to two. Patients must have no more than one prior line of systemic chemotherapy for advanced breast cancer. Patients may have received adjuvant or neoadjuvant taxane chemotherapy (docetaxel or paclitaxel), with an interval of at least 1 year prior to enrolment into this study. Exclusion criteria were patients who received 2 or more lines of chemotherapy in the metastatic setting, known hypersensitivity to taxane (docetaxel or paclitaxel), radiotherapy within 4 weeks, and current severe or uncontrolled medical conditions that could limit the ability of the patients to receive systemic chemotherapy.

Treatment

All the 10 patients received 50mg/m^2 docetaxel on day 1 of a 2-week cycle. Each dose of docetaxel was administered intravenously over 60 minutes. They received oral dexamethasone 8mg twice daily for 3 days starting 1 day prior to docetaxel. Granulocyte colony-stimulating factors were not recommended and only used in case of febrile neutropenia. Dose reduction of docetaxel was allowed if there were unacceptable adverse events from 50mg/m^2 to 40mg/m^2. Dosing was delayed until recovery from any serious adverse events. Docetaxel was stopped at completion of 8 cycles, evidence of disease progression, intolerable toxicity or death. The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 4.0. Tumour assessments by CT scan of the thorax, abdomen and pelvis were performed at baseline, between cycle 4 and cycle 5, and after cycle 8, based on RECIST criteria. Quality of life was assessed with the EORTC QLQ questionnaire at baseline, every 4 weeks during treatment and at the end of study. After discontinuation of docetaxel, participants were followed up every 2 to 3 months until disease progression or death.

Statistical analysis

The primary endpoint was treatment safety. The secondary endpoints were tumour response and progression free survival (calculated from start of treatment to the date of event defined as the first documented progression or death due to any cause analysed with SPSS V20).

Ethical consideration

This study was approved by the Universiti Kebangsaan Malaysia Research Ethics Committee. An informed and written consent was obtained from all the participant in the study.

RESULTS

Between November 2017 and June 2018, 10 patients were recruited into this study and commenced on 2-weekly docetaxel. The baseline characteristics of the patients are shown in table I. Five patients completed all 8 cycles of docetaxel, meanwhile one patient received 7 cycles, two patients received 6 cycles, one patient received 5 cycles and one patient received 4 cycles. Median number of docetaxel cycles per patient was 6.5. The causes of stopping docetaxel were disease progression (20%), intolerable toxicity (20%) and death (10%).

Adverse events that were reported of at least 20 percent of patients are presented in Table II. There was one patient who developed febrile neutropenia who eventually died during the same hospital admission. This particular patient passed away due to respiratory failure secondary to community acquired pneumonia.

Overall response rate was reported to be 20%. Progression free survival (PFS) ranged from 2.1 months to 12.67 months with the median PFS reported to be 5.0 months. There were no significant changes in the quality of life reported via the EORTC QLQ questionnaire.

DISCUSSION

This study explores an alternative schedule of docetaxel for advanced breast cancer (ABC). To our knowledge, there are currently no published data of any phase two or three clinical trials investigating the role of two-weekly docetaxel in ABC. Two-weekly docetaxel appear to cause lower rate of febrile neutropenia compared to the reported data for 3-weekly regimen.

Treatment safety is an important factor for the selection of chemotherapy agent and its dose intensity. The aim of treatment is palliation of symptoms with minimal adverse events. In our study, the neutropenia rate was 90%, however febrile neutropenia rate was 10%. The frequency of neutropenia was higher than expected. However, the incidence of febrile neutropenia was still lower than

Table I: Demographic and baseline characteristics

Median (range) age (years)	**63 (46-69)**
ECOG performance status score	
0	4 (40%)
1	5 (50%)
2	1 (10%)
ER and PR status	
ER and/or PR positive	8 (80%)
ER and PR negative	1 (10%)
Unknown	1 (10%)
HER2 (combined IHC and SISH tests)	
Positive	3 (30%)
Negative	4 (40%)
Equivocal	1 (10%)
Unknown	2 (20%)
Triple Negative disease	
Visceral disease	
Yes	7 (70%)
No	3 (30%)
Most common disease sites	
Bone	4 (40%)
Lung	7 (70%)
Liver	4 (40%)
Lymph nodes	7 (70%)
Chemotherapy in the metastatic setting	
First line	4 (40%)
Second line	6 (60%)

Table II: Adverse events

N=10	Grade 1-2	Grade 3-4
Haematological		
Anaemia	10 (100%)	-
Neutropenia	7 (70%)	2 (20%)
Leucopoenia	4 (40%)	2 (20%)
Febrile neutropenia	-	1 (10%)
Non-haematological		
Lethargy	7 (70%)	-
Nausea	5 (50%)	-
Mucositis	3 (30%)	-
Peripheral neuropathy	3 (30%)	-
Vomiting	3 (30%)	-
Alopecia	2 (20%)	-
Diarrhoea	2 (20%)	-
Dizziness	2 (20%)	-
Hand-foot syndrome	2 (20%)	-
Pain	2 (20%)	-
Raised ALT	2 (20%)	-
Weight loss	2 (20%)	-

* ALT: Alanine amino transferase

Table III: RECIST response

Patients, n (%)	N=10
Complete response (CR)	-
Partial response (PR)	2 (20%)
Stable disease (SD)	5 (50%)
Disease progression (PD)	2 (20%)
Unknown	1 (10%)
Overall response rate	2 (20%)

reported rates for the 3-weekly regimen which is 14.3%.[6] Besides that, most other adverse events were grade 1 or 2 and easily managed.

The phase 3 trial comparing 2-weekly and 3-weekly docetaxel for prostate cancer did not permit the use of granulocyte colony-stimulating factor (GCSF).[11] We did not allow use of prophylactic GCSF except for treatment of severe neutropenia. Prophylactic GSCF is not widely used for patients with metastatic breast cancer in Malaysia.

Numerous phase 3 clinical trials compared docetaxel at 100mg/m^2 every 3 weeks with other chemotherapy agents including doxorubicin, paclitaxel, fluorouracil plus vinorelbine. These trials showed similar efficacy between these agents. The reported overall response rate (ORR) are 30.0-47.8%, median progression-free survival (PFS) of 4.4-6.5 months and median overall survival of 10.4-16.0 months.[15-19] Despite having a small sample size, the trend of ORR and PFS in our patients seems to be fairly similar to the reported studies.

This preliminary study was conducted prior to embarking onto a larger scale trial. This is to assess the feasibility of this treatment in the bigger group of patients and provide early safety profile of this regimen. Thus, a small sample size was chosen which was limited by manpower, research grant and time. This sample size is not powered to establish superiority over the 3-weekly docetaxel regimen. The authors suggest to wait for the results of phase three randomised controlled trials prior to using this 2-weekly regimen.

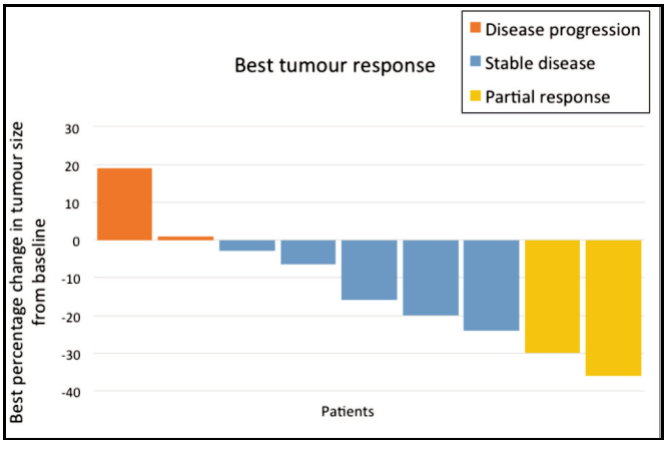

Fig. 1: Waterfall plot of best clinical response (RECIST 1.1) post treatment

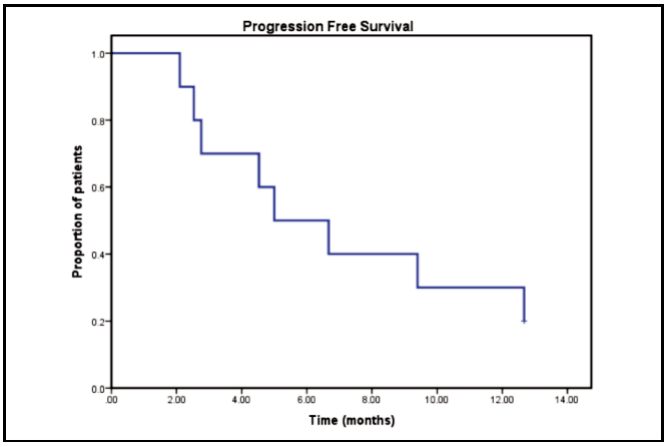

Fig. 2: Kaplan-Meier curve of progression free survival

CONCLUSION

This study concludes that docetaxel administered at 50mg/m^2 every 2 weeks may be reasonably safe and efficacious in patients with metastatic breast cancer in the first-line or second-line setting. In our experience the febrile neutropenia rate was 10% and the objective response rate (complete response or partial response) was 20%. The 2-weekly docetaxel regimen may be feasible in the Malaysian population pending a larger scale research such as a phase two or three randomised controlled trial. This regimen could potentially offer an alternative dosing schedule for docetaxel with lower risk of febrile neutropenia without compromising the efficacy in terms of response rate and progress-free survival. This could also contribute to the reduction of morbidity and mortality associated with febrile neutropenia or other docetaxel related adverse events.

CONFLICTS OF INTERESTS

There are no perceived conflicts of interest for the authors of this manuscript.

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