RESEARCH ARTICLE

Risk of Treatment Related Death and Febrile Neutropaenia with Taxane-Based Adjuvant Chemotherapy for Breast Cancer in a Middle Income Country Outside a Clinical Trial Setting

Chee Ee Phua[1]*, Anita Zarina Bustam[1], Mastura Md Yusof[1], Marniza Saad[1], Cheng-Har Yip[2], Nor Aishah Taib[2], Char Hong Ng[2], Yew Ching Teh[2]

Abstract

Background: The risk of treatment-related death (TRD) and febrile neutropaenia (FN) with adjuvant taxane-based chemotherapy for early breast cancer is unknown in Malaysia despite its widespread usage in recent years. This study aims to determine these rates in patients treated in University Malaya Medical Centre (UMMC). Patients and Methods: Patients who were treated with adjuvant taxane-based chemotherapy for early breast cancer stages I, II or III from 2007-2011 in UMMC were identified from our UMMC Breast Cancer Registry. The TRD and FN rates were then determined retrospectively from medical records. TRD was defined as death occurring during or within 30 days of completing chemotherapy as a consequence of the chemotherapy treatment. FN was defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count <0.5x10^9/L, or expected to fall below 0.5x10^9/L. Results: A total of 622 patients received adjuvant chemotherapy during this period. Of these patients 209 (33.6%) received taxane-based chemotherapy. 4 taxane-based regimens were used namely the FEC-D, TC, TAC and AC-PCX regimens. The commonest regimen employed was the FEC-D regimen accounting for 79.9% of the patients. The FN rate was 10% and there was no TRD. Conclusion: Adjuvant taxane-based chemotherapy in UMMC for early breast cancer has a FN rate of 10%. Primary prophylactic G-CSF should be considered for patients with any additional risk factor for FN.

Keywords: Treatment related death (TRD) - febrile neutropaenia (FN) - breast cancer - adjuvant chemotherapy

Asian Pacific J Cancer Prev, **13 (9)**, 4623-4626

Introduction

Taxane-based adjuvant chemotherapy has come into the forefront of the armamentarium of chemotherapy available for breast cancer. In fact, the commonest role of chemotherapy given in most oncology centers is as adjuvant treatment for operable breast cancer. The Early Breast Cancer Triallists' Collaborative Group (EBCTCG) which involves collaborative meta-analyses undertaken on 194 unconfounded randomized trials of adjuvant chemotherapy or hormonal therapy that began by 1995, has found a marked absolute reduction in the 15 year breast cancer mortality rate with the use of adjuvant chemotherapy. It estimated an absolute reduction of 5%, 9% and 15% in breast cancer mortality at 15 years for patients younger than 50 years old with low, intermediate and high risk respectively. For patients who were 50-69 years old, the absolute reduction were 2%, 4% and 7% with low, intermediate and high risk respectively (EBCTCG, 2005). With the recent introduction of taxane-based chemotherapy, further improvement in overall survival can be achieved. This is in view of the findings of a comprehensive systematic review by the Cochrane group on taxanes for adjuvant treatment of early breast cancer published in 2010. It found a hazard ratio for death of 0.81 (95%CI 0.75-0.88, P<0.00001) favouring taxane-based regimens over non taxane-based regimens (Ferguson et al., 2010). However, with the widespread usage of these new regimens clinicians need to be cognizant of the increased risk of treatment-related death (TRD) and febrile neutropaenia (FN). There is still a paucity of real life clinical experience with regards to the risk of TRD and FN with taxane-based chemotherapy used in this setting outside of clinical trials. Certainly, there is no known published data on this issue in Malaysia. A study in University Malaya Medical Centre (UMMC) on adjuvant chemotherapy for breast cancer based on 1,317 patients treated from 2000-2007 revealed a TRD rate of 0.1% but the majority of patients were treated with non-taxane based chemotherapy and the FN rate was not reported (Phua et al., 2012).

Results from published phase 3 trials on taxane-based chemotherapy have shown a wide range of TRD and FN rates. In a landmark phase 3 study for taxane-based regimen, PACS 01 trial compared the FEC regimen (5-Fluorouracil, Epirubicin, Cyclophosphamide) for

*[1]Clinical Oncology Unit, [2]Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia *For correspondence: vince_phua@yahoo.com*

6 cycles with the FEC-D regimen (FEC3-Docetaxel3) involving 996 patients in the FEC arm and 1,003 patients in the FEC-D arm. There was a high rate of febrile neutropaenia at 8.4% and 11.2% in the FEC and FEC-D arms respectively. However, there was no TRD in both arms (Roche et al., 2006). In another study evaluating sequential docetaxel as adjuvant chemotherapy for breast cancer (TACT), the TRD rate was 0.3% for the FEC4-D4 regimen (FECx4-Docetaxelx4) while the control arm using 4 cycles of epirubicin 100 mg/m^2 followed by CMF regimen for another 4 cycles (E-CMF) had a TRD of 0.1% while another control arm using FEC for 8 cycles had no TRD. The rates of FN were 7%, 4% and 2% for the FEC4-D4, E-CMF and FEC8 regimens respectively (Ellis et al., 2009). The US Oncology Research group reported a TRD of 0.4% with the TC regimen comprising 4 cycles of Docetaxel and Cyclophosphamide and there was no TRD in the control arm using the AC regimen for 4 cycles (adriamycin and cyclophosphamide) in its phase 3 trial involving 1016 patients. The FN rates were 5% and 2% for the TC and AC regimens respectively. However, for elderly patients above 65 years, the rate of FN was higher at 8% for the TC regimen and 4% for the AC regimen (Jones et al., 2009). Another commonly used regimen is the ACx4 followed by Paclitaxelx4 regimen (AC-PTX). This regimen was compared to the ACx4 regimen in the NSABP-28 trial for node-positive breast cancer in the adjuvant setting. The TRD rates were 0.1% for the AC-PTX regimen and 0.3% for the ACx4 regimen. This trial reported a 4% FN rate during the 4 cycles of paclitaxel chemotherapy but did not report the FN rates specifically for the 2 comparison arms (Mamounas et al., 2005). Another study utilizing this regimen is the CALGB 9344 study which showed a TRD rate of 0.06% for the AC regimen while the AC-PTX regimen had a TRD rate of 0.13% (Henderson et al., 2003). However, the FN rates were not specifically reported. In a trial involving 1,491 patients with node positive breast cancer patients post definitive surgery, 745 patients received adjuvant TAC (Docetaxel, Adriamycin, Cyclophosphamide) and 746 patients received FAC (5-Fluorouracil, Adriamycin, Cyclophosphamide). The TRDs for the TAC group and FAC group was similar at 0.3%. However, the FN rate was very high at 24.7% for the TAC regimen in contrast to only 2.5% for the FAC regimen (Martin et al., 2005). So far, the results of all these large phase 3 randomized controlled trials using a taxane-based regimen have shown a TRD rate ranging from 0%-0.4% while the FN rate ranges from 4% to as high as 24.7%.

The only available large study on the rates of TRD and FN in a real life clinical setting for adjuvant taxane-based adjuvant chemotherapy for early breast cancer comes from a study conducted in four Ontario regional cancer centers. This study had 671 patients who utilized the FEC-D regimen and showed a TRD rate of 0.4% and a FN rate of 22.7% (Madarnas et al., 2011). The authors concluded that primary usage of haematopoietic growth factor should be considered in view of the high FN rate. As the usage of taxane-based regimen in the adjuvant setting for our early breast cancer patients has become increasingly common, we need data from our centre to determine these rates to guide our management. This study aims to determine the TRD and FN rates with taxane-based regimens in our center.

Materials and Methods

The data from the UMMC Breast Cancer Registry, which was started in 1993 and where data on basic demography, clinical and pathological tumour profile, treatment details and survival was prospectively collected, was used for this study. We reviewed all patients prescribed with adjuvant chemotherapy using taxane-based chemotherapy for early-stage breast cancer in our centre from 1st January 2007 till 31st December 2011 retrospectively for the presence of FN and TRD. The aim of this study is to establish the early TRD rate and the FN rate with these chemotherapy regimens. Treatment-related death is defined as death occurring during or within 30 days of completing chemotherapy as a consequence of the chemotherapy treatment. Febrile neutropaenia is defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count <0.5 x 10^9/L, or expected to fall below 0.5 x 10^9/L (de Naurois et al., 2010).

Results

Between 1st January 2007 and 31st December 2011, 622 patients with newly diagnosed breast cancer received adjuvant chemotherapy for either AJCC stage I, II or III diseases. Of these patients, 209 received taxane-based chemotherapy (33.6%). None of these patients received primary prophylactic G-CSF. Analysis was therefore

Table 1. The Cohort of 209 Patients

Items		No. of patients	%
Age	<50 years	110	52.6
	51-69 years	93	44.4
	>70 years	6	3
Gender	Female	209	100
Race	Malay	58	27.8
	Chinese	118	56.5
	Indian	31	14.8
	Others	2	0.9
Tumour Stage	TI	61	29.2
	T2	106	50.7
	T3	25	11.9
	T4	17	8.2
Nodal Stage	N0	45	21.5
	N1	72	34.4
	N2	38	18.2
	N3	54	25.9
AJCC stage	I	19	9.1
	II	129	61.7
	III	61	29.2
ER Status	Positive	136	65.1
	Negative	73	34.9
HER-2 Status	Positive	103	49.3
	Negative	106	50.7
Chemotherapy Regime	FECx3-Dx3	167	79.9
	ACx4-Paclitaxelx4	5	2.4
	TACx6	6	2.9
	TCx4	31	14.8

performed on these 209 patients. Baseline characteristics including clinicopathological and the different taxane-based regimens utilized are summarized in Table 1. The commonest taxane-based adjuvant chemotherapy regimen used was the FEC-D regimen (3 cycles of 5-Fluorouracil 500 mg/m^2,Epirubicin 100 mg/m^2,Cyclophosphamide 500 mg/m^2 followed by 3 cycles of Docetaxel 100 mg/m^2) accounting for 79.9% of patients. This was followed by the TC regimen (Docetaxel 75 mg/m^2,Cyclophosphamide 600 mg/m^2 x 4 cycles) which was used in 14.8% of the patients. Two other regimens were employed which were the TAC regimen (Docetaxel 75 mg/m^2, Adriamycin 50 mg/m^2, Cyclophosphamide 500 mg/m^{2}x6 cycles) in 2.9% and the AC-PCX regimen (Adriamycin 60 mg/m^2, Cyclophosphamide 600 mg/m^{2}x4 cycles followed by Paclitaxel 175mg/m^{2}x4 cycles) in 2.4% of the patients.

There was no TRD in the 209 patients. However, the overall FN rate was high at 10% (21/209 patients). With the FEC-D regimen, 8.3% had FN (14/167 patients) and 3 patients had 2 episodes of FN. Ten out of the 17 episodes of FN occurred after the Docetaxel chemotherapy. With the TC regimen, 12.9% (4/31 patients) experienced FN. The TAC regimen had a very high rate of FN at 50% (3/6 patients) and one patient experienced 3 episodes of FN. No patient on the AC-PCX regimen developed FN (0/5 patient).

Discussion

The main result of this study is the FN rate of 10% with taxane-based adjuvant chemotherapy regimens for early breast cancer in our center. With increasing usage of taxane-based regimens, this FN rate can be used to guide our clinical practice with regards to our discussion with our patients when obtaining informed consent prior to adjuvant chemotherapy as FN is known to be associated with TRD. Although our study did not show any TRD, this cannot be taken as a true TRD measure as the patient number was small with only 209 patients. We feel a study should have at least 1,000 patients to give an acceptable TRD rate. Thus far, the only TRD rates we have to guide us are the rates from the randomized phase 3 trials mentioned earlier at 0-0.4%. Febrile neutropaenia is the most frequent and potentially lethal complication of adjuvant chemotherapy for breast cancer and it carries a mortality rate of at least 5% (de Naurois et al., 2010; Klastersky et al., 2011). Mortality rates are even higher when there is proven bacteraemia with 18% mortality rate in Gram-negative bacteraemia (de Naurois et al., 2010). As such a FN rate of 10% in our center must be taken seriously and patients must be adequately educated regarding this risk. A complete patient education system must be in place including the steps needed to be taken in the event of any fever or illness after adjuvant chemotherapy.

A simple cost analysis for the usage of primary prophylactic granulocyte colony-stimulating factor (G-CSF) in our center will cost RM4230 per patient assuming the commonest FEC-D regimen is used (RM235 per injection on D8-10 of each cycle). Meanwhile, admission to our center for an uncomplicated episode of FN will cost approximately RM1766 assuming 5 days of admission (RM 80 per day of admission) with routine blood investigations (Full blood count x3, renal profile x1, liver function test x1, blood culture and sensitivity x1) costing RM 91, urine culture and sensitivity RM 25, chest X-Ray RM25, 5 days of S/C G-CSF RM1175 and intravenous cefepime 2g three times a day RM450. However, this represents a gross underestimation of the actual cost as our center is heavily subsidized by the government. Assuming the usage of prophylactic G-CSF can reduce the rate of FN by 50%, if we start off with 100 patients, out of 100 patients treated only 5 patients will develop FN if prophylactic G-CSF is used (Dale, 2002; Lyman et al., 2002; Kuderer et al., 2007). The cost will be RM176.6 per patient without prophylactic G-CSF (10 patients with FN, 10xRM1766/100 patients). With the usage of prophylactic G-CSF, RM 4318.3 per patient (5 patients with FN, 5xRM1766/100 patients+RM4230) will be required. Another way of looking at it will be a calculation of the numbers needed to treat (NNT) to prevent an episode of FN. Assuming the risk of FN is 10% without prophylactic G-CSF as shown in our study and prophylactic G-CSF can reduce this rate to 5% then the NNT will be 20 (100/10-5). The cost will be RM84600 per FN prevented (20xRM4230).

This cost is highly prohibitive in our setting to be used routinely. It is also not difficult to understand why multiple guidelines including the ASCO, NCCN, EORTC and ESMO have suggested for usage of primary prophylactic G-CSF only if the risk of FN exceeds 20% (Aapro et al., 2006; Smith et al., 2006; Greil and Psenak, 2007; NCCN, 2009). When using a chemotherapy regimen with an intermediate risk of FN of 10-20% which is the rate that our center is facing, particular attention should be given to patient related risk factors that may increase the overall risk of FN (Aapro et al., 2011). A number of patient related risk factors that increases the risk of FN have been described including advanced age of ≥65 years, co-morbidity and performance status (Crawford et al., 2004; Srokowski et al., 2009; Aapro et al., 2011). Clinicians need to pay particular attention to any patient that has any co-morbidity, performance status more than ECOG 0 or those ≥65 years undergoing taxane-based adjuvant chemotherapy for early breast cancer. The pros and cons of using primary prophylactic G-CSF must be discussed thoroughly with these patients as the risks of FN and even TRD though very low are very real. A TRD in an adjuvant setting should be avoided at all cost if at all possible and any risk minimization strategy available must be discussed just as the potential survival benefit of adjuvant chemotherapy is taken into account when making a decision on whether to proceed with adjuvant chemotherapy or not.

In conclusion, the FN rate in our center for taxane-based chemotherapy in the setting of adjuvant chemotherapy for breast cancer was high at 10%. However, there was no TRD. Primary prophylactic G-CSF should be considered especially if a patient has additional risk factor for FN.

Acknowledgements

This study was supported by a HIR Grant UM.C/

HlR/MOHE/06 from the Ministry of Higher Education, Malaysia

References

Aapro MS, Bohlius J, Cameron DA, et al (2011). 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy –induced febrile neutropaenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*, **47**, 8-32.

Aapro MS, Cameron DA, Pettengell, et al (2006). EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropaenia in adult patients with lymphomas and solid tumours. *Eur J Cancer*, **42**, 2433-53.

Crawford J, Dale D, Lyman G (2004). Chemotherapy-induced neutropaenia. Risks, consequences and new directions for its management. *Cancer*, **100**, 228-37.

Dale DC (2002). Colony-stimulating factors for the management of neutropaenia in cancer patients. *Drugs*, **62**, 1-15.

de Naurois J, Novitzky-Basso I, Gill MJ, et al (2010). Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Annals of Oncology*, **21**, 252-6.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. *Lancet*, **365**, 1687-717

Ellis P, Barrett-Lee P, Johnson L, et al (2009). Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open label, phase III, randomized controlled trial. *Lancet*, **373**, 1681-92.

Ferguson T, Wilcken N, Vagg R, et al (2010). Taxanes for adjuvant treatment of early breast cancer (Review). The Cochrane Cochrane Library, Issue 10.

Greil R, Psenak O (2007). Hematopoietic growth factors: ESMO recommendations for the application. *Ann Oncol*, **18**, 89-91.

Henderson IC, Berry DA, Demetri GD, et al (2003). Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol*, **21**, 976-83.

Jones S, Holmes FA, O'Shaughnessy J, et al (2009). Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol*, **27**, 1177-83.

Klastersky J, Awada A, Paesmans M, et al (2011). Febrile neutropaenia: A critical review of the initial management. *Critical Reviews in Oncology/Hematology*, **78**, 185-94.

Kuderer NM, Dale DC, Crawford J, et al (2007). Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropaenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol*, **25**, 3158-67.

Lyman GH, Kuderer NM, Djulbegovic B (2002). Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: meta-analysis. *Am J Med*, **112**, 406-11.

Madarnas Y, Dent SF, Husain SF, et al (2011). Real world experience with adjuvant FEC_D chemotherapy in four Ontario regional cancer centers. *Current Oncology*, **18**, 119-25.

Mamounas EP, Bryant J, Lembersky B, et al (2005). Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP-28. *J Clin Oncol*, **23**, 3686-96.

Martin M, Pienkowski T, Mackey J, et al (2005). Adjuvant Docetaxel for node positive breast cancer. *N Engl J Med*, **352**, 2302-13.

National Comprehensive Cancer Network (2009). Myeloid growth factors. http://www.nccn.org/

Phua CE, Bustam AZ, Yusof MM, et al (2012). Risk of treatment related death (TRD) with adjuvant chemotherapy for breast cancer: A study in University Malaya Medical Centre (UMMC). *J Cancer Therapeutics and Res*, **1**, 13.

Smith TJ, Khatcheressian J, Lyman JH, et al (2006). Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*, **24**, 3187-205.

Srokowski TP, Fang S, Hortobagyi GN, et al (2009). Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *J Clin Oncol*, **27**, 2170-6.