

## RESEARCH ARTICLE

# Risk of Treatment Related Death and Febrile Neutropaenia with First Line Palliative Chemotherapy for De Novo Metastatic Breast Cancer in Clinical Practice in a Middle Resource Country

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## Abstract

**Background:** The risk of febrile neutropaenia (FN) and treatment related death (TRD) with first line palliative chemotherapy for de novo metastatic breast cancer (MBC) remains unknown outside of a clinical trial setting despite its widespread usage. This study aimed to determine rates in a large cohort of patients treated in the University of Malaya Medical Centre (UMMC). **Materials and Methods:** Patients who were treated with first line palliative chemotherapy for de novo MBC from 2002-2011 in UMMC were identified from the UMMC Breast Cancer Registry. Information collected included patient demographics, histopathological features, treatment received, including the different chemotherapy regimens, and presence of FN and TRD. FN was defined as an oral temperature  $>38.5^{\circ}\text{C}$  or two consecutive readings of  $>38.0^{\circ}\text{C}$  for 2 hours and an absolute neutrophil count  $<0.5 \times 10^9/\text{L}$ , or expected to fall below  $0.5 \times 10^9/\text{L}$  (de Naurois et al, 2010). TRD was defined as death occurring during or within 30 days of the last chemotherapy treatment, as a consequence of the chemotherapy treatment. Statistical analysis was performed using the SPSS version 18.0 software. Survival probabilities were estimated using the Kaplan-Meier method and differences in survival compared using log-rank test. **Results:** Between 1<sup>st</sup> January 2002 and 31<sup>st</sup> December 2011, 424 patients with MBC were treated in UMMC. A total of 186 out of 221 patients with de novo MBC who received first line palliative chemotherapy were analyzed. The mean age of patients in this study was 49.5 years (range 24 to 74 years). Biologically, ER status was negative in 54.4% of patients and Her-2 status was positive in 31.1%. A 5-flourouracil, epirubicin and cyclophosphamide (FEC) chemotherapy regimen was chosen for 86.6% of the cases. Most patients had multiple metastatic sites (58.6%). The main result of this study showed a FN rate of 5.9% and TRD rate of 3.2%. The median survival (MS) for the entire cohort was 19 months. For those with multiple metastatic sites, liver only, lung only, bone only and brain only metastatic sites, the MS was 18, 24, 19, 24 and 8 months respectively (p-value= 0.319). **Conclusions:** In conclusion, we surmise that FEC is a safe regimen with acceptable FN and TRD rates for de novo MBC.

**Keywords:** De novo metastatic breast cancer - palliative chemotherapy - febrile neutropaenia - treatment related death

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## Introduction

Approximately 6-10% of new breast cancer cases are Stage IV or metastatic at first diagnosis. This is sometimes called “de novo” metastatic disease, meaning from the beginning according to data taken from the United States (DeSantis et al., 2011). However, data from Asian countries suggest the rate to be much higher, approaching 10% to 25% (Chopra et al., 2001; Tan et al., 2005; Yip et al., 2006; Lim et al., 2007). In addition, Asian patients present with larger metastatic tumours and often involve multiple metastatic sites (Agarwal et al., 2007). The median survival of de novo metastatic breast cancer (MBC) is unknown as most reported studies included

patients who developed metastatic disease after initial treatment for early breast cancer. Median survival rates for MBC range from 1-4 years according to published data (Todd et al., 1983; Chang et al., 2003; Andre et al., 2004; Tai et al., 2004; Largillier et al., 2008; Ly BH et al., 2010; Perez-Fidalgo et al., 2011; Khodari et al., 2013). Treatment for de novo MBC and MBC due to recurrent disease is essentially the same but the prognosis may be different. Systemic treatment remains the mainstay of treatment and this includes chemotherapy, endocrine therapy and/or targeted therapy besides palliative care. For patients with large tumour burden and symptomatic from rapidly progressive disease, chemotherapy is usually employed initially to obtain a rapid control of the

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disease. However, chemotherapy is a toxic agent which may cause complications including febrile neutropaenia (FN) and not uncommonly treatment related death (TRD). Informing patients that the risk of TRD is negligible or less than one percent which is the figure often quoted by clinicians may be inadequate as this gives the impression that it is extremely rare. Moreover, less than 1% can mean anywhere between 0.9%, 0.1%, 0.01%, 0.001% and so forth. Patients deserve to fully understand the real risk of TRD and equally important is the need for clinicians to realize that TRDs are much commoner than perceived. There are various definitions of TRD used in the literature. For the purpose of this study the TRD was defined as deaths that occurred less than or equal to 30 days after the last cycle of chemotherapy, death of which was due to the chemotherapy itself. This definition was chosen as it was commonly used in many reported phase 3 trials and it is the least ambiguous amongst all definitions encountered in the literature. While in the adjuvant setting, clinicians and patients expect a low risk of FN and TRD, in the metastatic setting the expected rates should be higher as patients are either symptomatic or without further treatment can expect to become symptomatic soon and eventually die of metastatic disease. Reported FN rates in the literature from clinical trials for first line chemotherapy in MBC range from 4.9% to as high as 47.8% (Biganzoli et al., 2002; Alba et al., 2004; Conte et al., 2004; Cresta et al., 2004; Park et al., 2010; Tomova et al., 2010, Chan A et al., 2011). These rates differed according to different regimens and were the highest for regimens using combination chemotherapy rather than sequential treatment. Combination of adriamycin and taxane, both of which are the standard chemotherapy backbone for breast cancer, is especially toxic, with FN rates of 32% (adriamycin plus paclitaxel) and 47.8% (adriamycin plus docetaxel) in two phase III clinical trials (Biganzoli et al., 2002; Alba et al., 2004). Interestingly, a recent Cochrane meta-analysis has shown no improvement of overall survival (OS) when comparing combination therapy over sequential therapy for MBC. In fact, combination chemotherapy was shown to have a detrimental effect on progression free survival and increased rates of FN (Dear et al., 2013). The available data on TRD from clinical trials with chemotherapy for MBC range from 0.4% to 5.3% (Baker et al., 1974; Chlebowski et al., 1989; FESG, 2000; Biganzoli et al., 2002; Alba et al., 2004; Conte et al., 2004; Cresta et al., 2004; Park et al., 2010; Tomova et al., 2010, Chan A et al., 2011). Due to the paucity of data regarding the FN and TRD rates for de novo MBC especially in the clinical practice setting where we can expect a higher rate compared to clinical trial setting. In addition, it is not routine practice in our institution to institute growth factors with chemotherapy due to the cost incurred. Hence, we aim to study the rates of FN and TRD in our institution.

## Materials and Methods

The data from the University Malaya Medical Centre (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 the clinical notes of all patients prescribed with palliative chemotherapy for de novo metastatic breast cancer in our center from 1st January 2002 till 31st December 2011. Information collected included patient demographics, histopathological features, treatment received including the different chemotherapy regimens and presence of FN and TRD. The ER, PR and Her-2 status was measured using immunohistochemistry. Only Her-2 3+ were considered as Her-2 positive. The aim of this study is to establish the FN and TRD rate with first

**Table 1. The Clinicopathological Characteristics of the 186 Patients with Denovo Metastatic Breast Cancer who Underwent Palliative Chemotherapy**

Items	No. of patients	%
Age		
Up to 50 years	87	46.8
51 - 69 years	96	51.6
70 years and above	3	1.6
Race		
Malay	59	31.7
Chinese	99	53.2
Indian	28	15.1
Tumour Stage		
T1	11	5.9
T2	32	49.9
T3	64	11.6
T4	79	11.8
Nodal Stage		
N0	36	19.4
N1	81	43.5
N2	39	20.9
N3	30	16.2
ER Status		
Positive	85	45.6
Negative	101	54.4
PR Status		
Positive	58	31.1
Negative	128	68.8
HER-2 Status		
Positive	70	37.6
Negative	116	62.4
Histology		
Infiltrating ductal carcinoma	171	91.9
Infiltrating lobular carcinoma	7	3.8
Others	8	4.3
Grade		
Moderate	82	44.1
Poor	104	55.9
Site of Metastases		
Liver only	13	7
Lung only	35	18.9
Bone only	26	13.9
Brain only	3	1.6
Multiple ( $\geq 2$ sites)	109	58.6
Chemotherapy Regimen		
FEC	161	86.6
FEC-Docetaxel	2	1.1
Docetaxel alone	5	2.7
Paclitaxel alone	2	1.1
Capecitabine alone	4	2.2
CMF (Cyclophosphamide, Methotrexate, 5-FU)	2	1.1
AC (Adriamycin, Cyclophosphamide)	3	1.6
Others	7	3.7

line palliative chemotherapy for de novo MBC in our center. FN is defined as an oral temperature  $>38.5^{\circ}\text{C}$  or two consecutive readings of  $>38.0^{\circ}\text{C}$  for 2 hours and an absolute neutrophil count  $<0.5 \times 10^9/\text{L}$ , or expected to fall below  $0.5 \times 10^9/\text{L}$  (de Naurois et al., 2010). TRD is defined as death occurring during or within 30 days of last chemotherapy treatment as a consequence of the chemotherapy treatment. Statistical analysis was performed using the SPSS version 18.0 software. Survival probabilities were estimated using the Kaplan-Meier method and differences in survival compared using log-rank test.

## Results

Between 1st January 2002 and 31st December 2011, 424 patients with MBC were treated in UMMC. There were 221 patients with de novo MBC. A total of 186 of these patients received first line palliative chemotherapy for de novo MBC. Analysis was therefore performed on these 186 patients. Baseline characteristics including clinicopathological and treatment modalities utilized are summarized in Table 1. The mean age of patients in this study was 49.5 years (range 24 to 74 years). Biologically, ER status was negative in 54.4% of patients and Her-2 status was positive in 31.1% of patients. Most patients had multiple metastatic sites (58.6%). 5-flourouracil, epirubicin and cyclophosphamide (FEC) chemotherapy regimen accounted for 86.6% of the cases. The main result of this study showed a FN rate of 5.9% (11/186). Ten patients developed FN after FEC regimen (10/161=6.2%) while another patient developed FN after AT (adriamycin, docetaxel) regimen. Only one patient was treated with the AT regimen and this patient developed 2 episodes of FN during the 6 cycles of chemotherapy given to her. The TRD rate was 3.2% (6/186). The median survival (MS) for entire cohort was 19 months. For those with multiple metastatic sites, liver only, lung only, bone only and brain only the MS was 18, 24, 19, 24 and 8 months respectively (p-value=0.319).

## Discussion

The main result of this study is the FN rate of 5.9%. This rate is relatively low compared to those reported in clinical trials (4.9% to 47.8%) especially when seen outside of clinical trial setting. Moreover, patients were not routinely treated with prophylactic G-CSF. The main regimen used in this study was the FEC regimen (86.6%) which is the standard first line chemotherapy regimen at our centre for de novo MBC patients who had no prior chemotherapy treatment. An earlier study in our institution on the rate of TRD based on 1317 patients treated with adjuvant chemotherapy for early breast cancer from 2000-2007 also showed 87.9% of patients were treated with the FEC regimen. However, this study did not report the FN rate in the adjuvant setting (Phua et al., 2012). A follow-up study in the same institution on 209 patients who were treated with adjuvant taxane-based chemotherapy for early breast cancer from 2007-2011 then revealed a FN rate of 10.0% (Phua et al., 2012). 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). It is reassuring for both clinicians and patients that the rate of FN is manageable especially when using the FEC regimen. This may not be true when a taxane is utilized as only 4.8% of our patient cohort had taxane as part of their first line chemotherapy treatment.

The TRD rate in this study was 3.2% which was consistent with the rates reported in clinical trials (0.4% to 5.3%). Our previous study in the adjuvant setting showed a TRD rate of 0.1% for 1317 patients, majority of whom were treated with the FEC regimen (Phua et al., 2012). We accept a higher rate of TRD in the metastatic setting in view that there is an urgent need to control the disease and palliate symptoms as without treatment these patients will most likely progress to death. Although, there is no level 1 evidence regarding the usage of palliative chemotherapy in improving survival, there is substantial circumstantial evidence suggesting significant survival benefit with palliative chemotherapy. Significant improvement of survival through different time periods and differences in survival between newer and older chemotherapy regimens provide some evidence arguing for early administration of palliative chemotherapy for MBC (Gennari et al., 2005; Chia et al., 2007; Dafni et al., 2010). It is no longer considered ethical to perform a randomized controlled trial using placebo or best supportive care as the standard arm for MBC. Older publications have estimated a MS of 12 months for MBC while newer ones have tended towards 24 months. It is always difficult to give an accurate prognosis as these studies included patients with all its heterogeneity with regards to clinicopathological features and also treatment utilized. However, for patients needing palliative chemotherapy for MBC a survival of 18-24 months is definitely achievable with the latest armamentarium of available treatment. The MS of our study group was 19 months. With these figures in mind, clinicians can have an honest discussion with patients and their family members regarding expectation of duration of survival and also possibility of FN and TRD. Generally, a TRD rate of between 2-5% is acceptable for a treatment that is expected to improve survival. Our TRD rate of 3.2% consists of patients who mostly underwent chemotherapy with the FEC regimen. It is the commonest regimen used in many different countries with proven safety and efficacy besides affordability.

We acknowledge the shortcomings associated with a retrospective study and we also did not look at progression free survival which is an accepted outcome measure in MBC and also quality of life. However, the two main endpoints of FN and TRD are endpoints that are not ambiguous in nature which can be easily elicited by checking the case notes. The survival data was also updated by obtaining the latest information from the Malaysian national registration department in 2014. Although a larger number of patients would give a better point estimate of these complications, the rarity

of de novo MBC treated in the real life clinical setting especially in a middle resource country adds credit to this study. More importantly, knowing the low rates of FN and TRD in our study gives us the confidence regarding the safety of palliative chemotherapy in de novo MBC. We are cognizant that this is applicable mainly to the FEC regimen. However, the FEC regimen is a widely used regimen in this part of the world and also in European countries. We are also not aware of any randomized controlled trial of other chemotherapy regimen that has shown superior OS compared to the FEC regimen in this particular setting. Moreover, a recent Cochrane systematic analysis has shown no benefit of combination therapy over sequential therapy for MBC (Dear et al., 2013). In conclusion, we surmise that FEC is a safe regimen as first line treatment with acceptable FN and TRD rates for de novo MBC.

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