ORIGINAL ARTICLE

WEIGHT CHANGES DURING CHEMOTHERAPY AND PROGNOSTIC OUTCOME IN BREAST CANCER: A PRELIMINARYASSESSMENT IN SINGLE CENTRE COHORT

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ABSTRACT

A concern in breast cancer involves changes in weight which may adversely affect the prognosis of patients. This study intended to evaluate weight changed uring chemotherapy and its association with prognostic outcome measured as event-free survival (EFS)among breast cancer patients. A total of63 women diagnosed with breast cancer and have been treated by anthracycline-based chemotherapy between 2005 and 2011were included.A weight change (WC) was calculated based on relative percentage of weight changes from baseline to post-chemotherapy and categorized into either weight change (WC >5%) or stable (±5% WC).Survival probabilities were estimated using the Kaplan-Meier (SPSS 20). Upon treatment completion, 42.9% of the women experienced weight changes. A small weight reduction was observed (61.1 ± 11.6kg to 60.2 ± 11.9kg; -0.8 ± 4.0kg; p=0.106). The median EFS of women who experienced weight change was shorter (median 61.0 months) compared to those who maintained their weight (median 89.0 months) (p=0.044). In this study, weight changes during breast cancer chemotherapy were associated with poorer prognosis in comparison to women who maintained their weight.

Keywords: *Breast cancer, Chemotherapy, Retrospective study, Weight changes*

INTRODUCTION

Previous studies suggest that weight changes during chemotherapy were associated with poorer prognosis for the cancer patients, both with weight gain[1] and weight loss[2]. Indeed, the degree of weight changes experienced by women following breast cancer diagnosis varies greatly, while in some women weight change is not evident[2,3]. In western population, limited evidence on this topic had so far documented inconsistent results and data was largely based on small sample studies (n=20-25). Freedman et al.[4]reported no weight change after completing chemotherapy treatment, while Aslani et al.[5] reported a significant increase of 2.35kg in mean body weight during treatment period. Weight gain was commonly reported in women receiving cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen[5-7], while it occurs less in women treated with anthracyclines regimen[4,8]. In Malaysia, previous studies have generally reported patterns of weight changes following breast cancer diagnosis[3,9], yet, none of these investigations have specifically examined weight changes during the primary phase of chemotherapy period.

A vital concernamong women with breast cancer is that fluctuations in body weight including weight gain or weight loss may adversely affect the risk of recurrence and possibly their survival. Findings from population-based studies have suggested that higher body mass index (BMI) or being overweight or obese at diagnosis has been associated with poorer prognosis[10]. However, there has been little research to date exploring whether weight changes during chemotherapy directly or indirectly influences breast cancer outcomes.

Furthermore, studies that evaluated factors relating to survival rates in our populations were mostly focusing on demographics and clinic-pathological variables[11-13], rarely examining body weight status particularly on weight changes or BMI. To our knowledge, this is the first study using the breast cancer database from a local public hospital located in the east-coast of Peninsular Malaysia assessing weight changes in relation to breast cancer prognosis. Research on this subject is important to better understand the role of body weight on breast cancer outcome hence developing future cancer control research that could improve the quality of life (QoL) and potentially the survival of women with breast cancer during treatment. As such, the aim of this study was to evaluate weight changes in women with breast cancer during anthracycline-based chemotherapy and its association with prognostic outcome measured as event-free survival (EFS).

METHODOLOGY

Study design and population

A study based on a hospital retrospective cohort has been conducted at Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu, Malaysia. The records of all registered breast cancer patients from the hospital cancer registry were retrieved. Data were then collected from the records of patients who had completed chemotherapy treatment between January 2005 and December 2011. In particular, patients who had histologically confirmed breast cancer, and received chemotherapy under the anthracycline-based chemotherapy regimen were selected. Only records containing complete information on tumor staging, therapy protocol, number of cycles, anthropometry data, i.e. weight and height and menopausal status were considered. The records were excluded if weight assessment did not include at least measurements at baseline and at the end of chemotherapy or if there was a history of another malignancy. A total of 219 files were reviewed. However, only63 were available for the final study analysis, while others are excluded due to either irretrievable or missing record otherwise incomplete weight data. Permission to conduct this study was obtained from Malaysia Ministry of Health's (MOH) Research and EthicsCommittee (MREC) (Ref. no: (2) dlm.KKM/NIHSEC/08/0804/P11-42).

Weight measurements

Information on body weight including date of measurement was extracted from reports of clinical examination, follow-up history, an aesthesiology reports and chemotherapy medication reports. Usually, weight was recorded at the hospital by a nurse at each chemotherapy visit starting from the beginning of treatment until the last chemotherapy cycle (every 21days for 6 cycles).Two different body weight variables were introduced for study analysis, i.e. baseline weight and weight after chemotherapy. Baseline weight was measured within one to three months before start of chemotherapy treatment. Weight after chemotherapy was defined as the last body weight measured in the period from one to three months after completing this systemic treatment.

For this current study, an absolute weight changes was defined as the difference in weight before and after chemotherapy administration. Additionally, a relative weight changes was defined as relative percent weight changes between weight measurements from baseline to post-chemotherapy treatment [(weight after chemotherapy –baseline weight / baseline weight) x 100]. The weight changes were later categorized into the following groups: weight changes (a relative weight loss or weight gain >5% between weight measurement from baseline to post-chemotherapy treatment) or stable (±5% weight changes). These categories of weight changes were chosen because a number of studies suggest that a 5% change in body weight is considered clinically meaningful[14].Concerning the assessment of weight changes over therapy cycle, only patients who completed the prescribed six cycles of chemotherapy were included in the analysis.

The administration ofchemotherapy regimens contain anthracyclines and/or taxanesfor six cycles was considered as an acceptable regime[3] and commonly being practisedat our local government hospital. Indeed, 36 women with breast cancer (60.3%) completed all prescribed chemotherapy cycles.

Clinical factors

Information on age of patients, menopausal status, hormonal receptors, disease stage, comorbid illness as well as treatment received before and after chemotherapy was also recorded. Commonly employed anthracycline regimens were fluorouracil, doxorubicin and cyclophosphamide (FAC), followed by fluorouracil, epirubicin and cyclophosphamide (FEC). If data on menopausal status was not available, patients were then categorized based on age, i.e. pre- menopausal if age at diagnosis was 50 years or younger, post-menopausal if age at diagnosis was 51 years or older. Additionally, the Body Mass Index (BMI) was calculated by dividing weight (kg) by height (m) squared. The different subclasses of patients were categorized as followed: underweight (< 18.5), normal (18.5 - 24.9), overweight (25.0 - 29.9) or obese (≥ 30.0)[15].

Prognostic outcomes

For the study analysis, prognostic outcome was described as event-free survival (EFS) and defined as the time interval (in months)between the estimated date of diagnosis to the first occurrence of any of the following events: recurrence of breast cancer at any site; second non-breast malignant disease or death from any cause[4,5]. Medical records were reviewed to verify the outcome. Survival time was calculated from the date of initial diagnosis to the date of last contact or last known to be alive. Reachable family members responding to a phone call has ascertained the last status report, whether the patient was alive or dead. The cut-off date for the follow-up for all patients was January 2013.

Statistical analysis

SPSS Version 20.0 (SPSS Inc., ChicagoIL, U.S.A.) was used for data compilation, and statistical analysis. Descriptive statistics wereapplied and presented as mean, median and percentages.The median was used to report body weight changes as the normality requirements were violated (Shapiro-wilk test= $p<0.05$; data was positively skewed). A dependent t-test was carried out to

assess whether there was a difference in weight before and after chemotherapy treatment. The Kaplan-Meier procedure was used to calculate survival whereas statistical differences between survival curves were analysed using the log-rank test. The level of significance was set at5% (2-sided).

RESULTS

Table 1 presents the main characteristics of the study population. The mean age at diagnosis was 50.1 ± 10.5 years. Of the total study population, majority were Malays (87.3%),diagnosed with cancer stage greater than Stage II (68%) and underwent mastectomy (95%). Over half of the women were post-menopausal at diagnosis (54.0%) and had no family history of malignancy (74.6%). All were treated with anthracycline-based regimen. None of the women received corticosteroids as a part of their chemotherapy regimens except for anti-nausea prophylaxis (5-TH_3 antagonist and dexamethasone).

Table1. Main characteristics of the study population (n=63)

Characteristics	n	%
Age at diagnosis (years)		50.1 ± 10.5†
<40	6	9.5
40 – 49	27	42.9
50 – 59	18	28.6
≥ 60	12	19.0
Ethnic group		
Malay	55	87.3
Chinese	8	12.7
Baseline BMI (kg/m^2)		
Underweight (<18.5)	3	4.8
Normal (18.5 – 24.9)	31	49.2
Overweight (25.0 – 29.9)	15	23.8
Obese (≥30)	14	22.2
Menopausal status at diagnosis		
Pre-menopausal	29	46.0
Post-menopausal	34	54.0
Comorbid illness		
Diabetes	2	3.3
Hypertension	12	19.0
Diabetes & Hypertension	13	20.6
None	36	57.1
Surgery		
Mastectomy	60	95.2
Lumpectomy	3	4.8
Stage		
I & II	20	31.7
III & IV	43	68.3
Oestrogen receptor		
Positive	14	22.2
Negative or unknown	49	77.8
Family history		
Yes	14	22.2
No	47	74.6
Unknown or missing	2	3.2
Treatment year(s)		
2005-2006	43	68.3
2007-2009	9	14.3
2010-2011	11	17.4
Chemotherapy regimen		
Cyclophosphamide + doxorubicin + fluorouracil (CAF)	29	46.0
Fluorouracil + epirubicin + cyclophosphamide (FEC)	24	38.1
Fluorouracil + epirubicin + cyclophosphamide + docetaxel (FEC-T)	4	6.3
Other anthracycline-based combinations	6	9.5

†*Mean ± standard deviation (sd)*

Overall, over half of the women were overweight or obese (56.0%) with a mean baseline BMI of 26.0 ± 5.0 kg/m^2. Upon treatment completion, majority of the women remained weight stable (57.1%).Only a small, non-significant weight reductionwas observed(61.1 ± 11.6kg to 60.2 ± 11.9kg; -0.8 ± 4.0kg; p=0.106).Still, a notable proportion of women experienced significant

weight changes whereby nearly one-third (27.0%) reported weight loss and another 15.9% of the women gained weight.During approximately 16 weeks of treatment period, a median weight loss of 6.0kg (range: -3.0 to -15.0kg) was recorded denoting about -7.81% relative weight changes (range:-31.2 to -5.2%)(Table 2). Apart from that, the median weight changes in 10 women that showed weight gain was 4.0kg (range: 3.0 to 5.5kg) with a relative weight change of 6.7% (range:5.7to 8.6%). Also, women with lower BMI mostly experienced weight gain compared to women who maintained or lost their weight.

Table 2.Weight status in women with breast cancer (n=63)

Variable	Weight changes		Weight stable ± 5% (n =36) Median (IqR)
	Loss >5% (n =17) Median (IqR)	Gain >5% (n =10) Median (IqR)	
Absolute weight changes (kg)	-6.0 (3.7)	4.0 (1.1)	0.0 (1.0)
Relative weight changes (%)	-7.7% (7.1)	6.7 (1.4)	0.0 (2.2)
Baseline BMI (kg/m^2)	25.0 (8.9)	24.0 (3.4)	24.9 (9.0)

IqR = Interquartile range

An irregular pattern of weight changes during chemotherapy period was noted (Fig.1). Indicated by negative weight changes, these women experienced weight reduction from their initial weight after the first cycle of chemotherapy (-0.4% ± 2.6). Continued the trend towards the second (-0.5% ± 3.4) and the third treatment cycle (-0.1% ± 5.2). However, women tended to regain the initial weight loss after the mid of treatment period (0.0% ± 5.7), but returned to the previous negative pattern towards the end of the treatment with a higher decrease (weight changes of -0.5% ± 6.4 and -0.7% ± 7.3 during the fifth and sixth chemotherapy cycle).

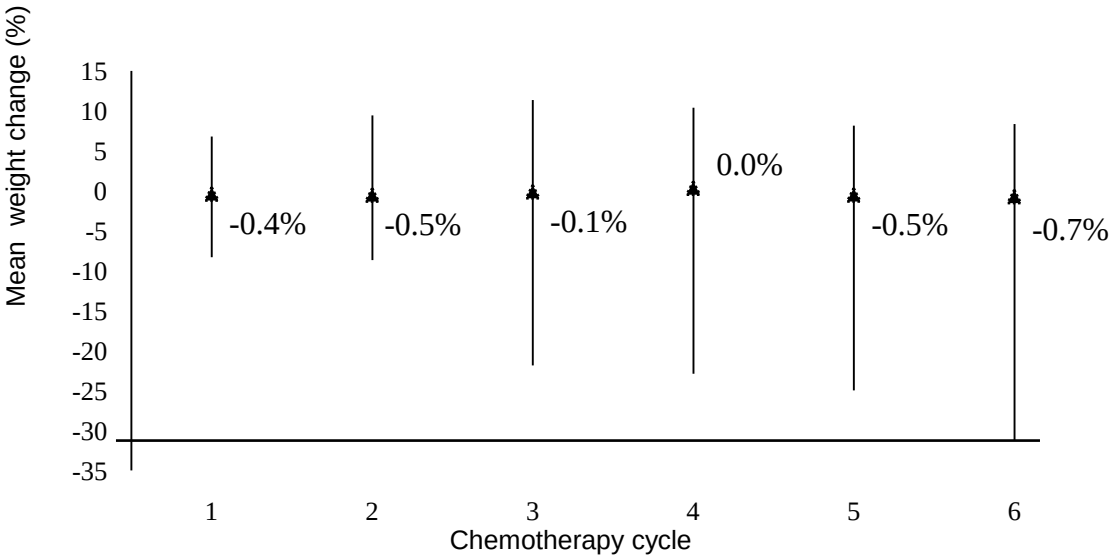

Fig 1 Mean relative weight changes(in percentage)during chemotherapy period

Within a median follow-up period of 45 months, 17womenhad recurrence, 11women died from breast cancer and 7women were lost to follow-up. The overall median EFS was84.0 month (95% CI 80.8, 87.2). Univariate analysis for EFS in this cohort revealed a significant EFS difference between women whose weight varied more than 5% compared to women who had stable weight (p=0.044) (Fig. 2).The median EFS of women who gained or lost weight was shorter (median 61.0 months) compared to those who maintained their weight (median 89.0 months).However, there was no evidence that EFS was influenced by BMI categories(p=0.301).

DISCUSSION

In a population of women with breast cancer who received anthracycline-based chemotherapy regimen, the magnitude and frequency of weight changes as well as its possible association with event-free survival (EFS) were evaluated. The present study is in agreement with previous findings by Freedman et al.[4]which have found

that there was a small, non-significant weight reduction observed in a group of twenty United State (US)women with breast cancer receiving anthracycline-based chemotherapy regimen. Demark-Wahnefried et al.[16]also reported that the body weight of twenty pre-menopausal American women receiving primarily anthracycline-based chemotherapy remained unchanged throughout the course of chemotherapy period. Evidence from several prospective studies suggested that weight gain was commonly associated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen[5, 6, 17]. However, a large longitudinal data from the women's healthy eating and living (WHEL) study assigning 3088 women identified as having breast cancer in the US between 1991 and 2000showed that no particular regimen was associated with a greater weight gain than the others[14].

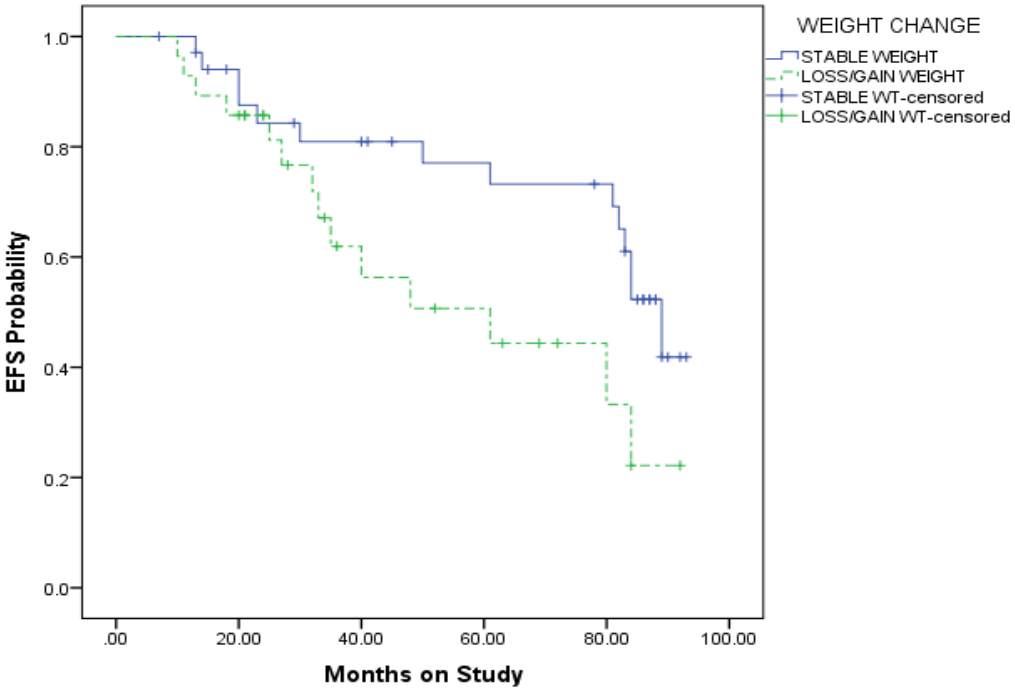

Fig 2. Kaplan-Meier estimate of Event-Free Survival (EFS) by weight variation

Other possible explanations for the lack of weight gain during chemotherapy may also be due to the inclusion of majority women with late stage of breast cancer plus the relatively shorter duration of chemotherapy administration. Delayed disease presentation was expected as it has been reported that the Malays whose covering almost 90% of our respondents tend to present at the advanced stage of the cancer[18,19]. On similar direction, a mean loss of 0.52 ± 1.21% (p=0.11) of body weight per month was observed during chemotherapy in the metastatic breast cancer group[20]. Concerning the follow-up period, a substantial number of studies that examined long term weight changes in women with breast cancer after chemotherapy reported that weight gain has been observed mostly at 6 and 12-month post-chemotherapy[7, 21-23]. Hence, it is possible that the assessment on weight variation within one to three months after chemotherapy may not have reflected any acute decrease or increase in the immediate post-chemotherapy period.

Of note, significant weight changes also occurred in our sample but to a lesser extent whereby nearly one third experienced weight loss and another 16% of the women gained weight. The weight variation found in the present study is even more remarkable given that the use of 'relative weight changes' may be a better measure of clinical importance than 'absolute changes' which was frequently being used in earlier studies. This finding may in part reflect a range of nutritional responses to chemotherapy within these groups. Increases in dietary intake associated with chemotherapy have previously been reported in breast cancer population[24, 23]. The increases in dietary intake were particularly observed during mid-treatment cycles[7, 25] which may be related to our respondents who tended to regain their initial weight after the third chemotherapy cycles. Chemotherapy-associated hungers, increased sense of well-being or increased snacking to offset nausea were thought to be the contributory factors for such patterns[26]. Indeed, psychological factors relating to the adjustment to the breast cancer diagnosis coupled with the excess stress from on-going chemotherapy may have interruptednormal eating patterns that kept diet and weight stable throughout the course of chemotherapy period[6].

Evidence on prognostic value of weight variation is mixed and not easily comparable. Most prior research documented an impact of weight gain on patient outcome. The largest data to-date

was from the Nurses' Health Study participants diagnosed with non-metastatic breast cancer (n= 5204). This study has found that weight gain was associated with an increased risk of recurrence, breast cancer death and total mortality, but only among never-smoking women[27]. However, the most recent findings conducted among European population evaluating the prognostic value of weight changes during anthracycline-based chemotherapy on non-metastatic breast cancer revealed that patients who had gained or lost weight (> 5% weight changes) was positively associated with an increased risk of both recurrence and death by comparison to patients who maintained their weight[28]. This result was intriguingly comparable to our finding which found some evidence that the median EFS of women who experienced weight changes was significantly shorter compared to women with no weight variation. Thivatet al.[28] had proposed that weight changes reflected a metabolic disorder altering energy expenditure equilibrium. Moreover, unfavourable changes in body composition with lean body loss even in the absence of an overall weight change indicating of sarcopenic obesity have been frequently documented[21, 22, 29]. All these adverse effects of weight changes may play a central role on different metabolic modifications induced by chemotherapy thereby predisposing patients to morbidity and mortality.

Apart from that, earlier literatures had documented that women who were overweight at the time of diagnosis have been associated with poorer survivals[30]. Excess body weight and BMI are established risk factors due to the fact that excess adipose tissue enhances circulating oestrogens. Epidemiologic and clinical data has demonstrated that increased or prolonged circulating oestrogen promotes the initiation and progression of breast cancer. Although some studies have reported shorter overall survival from breast cancer with BMI, there was no corresponding association between initial BMI and EFS in this study. This is largely could be due to limited samples and short follow-up time, thus diluting the impact of initial BMI status. Essentially, studies with sufficient study population sizes (n= 14,709[6], 2,887[7]) had reported that obese women with breast cancer had a poorer disease-free survival.

The strength of this study still remained in the usage of a population-based data which were the first primarily collected in a local public hospital in Terengganu that caters to the majority lower socioeconomic group and mainly Malay population. Therefore, the present study is rather novel in providing baseline data on weight changes and survival of women with breast cancer in this local population. There were several limitations to this study; nonetheless one potential restriction might be caused by the adoption of a retrospective study design (non-random sampling) and the involvement of only single recruitment centre which might therefore not be entirely representative of all chemotherapy breast cancer. Limited sample size also restrained adjustment for possible confounding factors related to weight changes such as age, BMI, menopausal status and disease stage. Still, this exploratory study has generated preliminary evidence on prognostic impact of weight changes on survival among the local breast cancer cohort to serve as a basis for future research. Consistent with our data and guidelines provided by the American Cancer Society[8],weight stabilization should therefore is an appropriate goal for women with breast cancer.

CONCLUSIONS

In summary, this preliminary assessment suggests that over 16-week duration of breast cancer chemotherapy, the weight changes were restricted to only a small, non-significant weight reduction. The current data further supported the argument that weight changes during anthracycline-based treatment in women with breast cancer was related topoorer prognosis with shorter EFS, in comparison to women who maintained their weight. A long-term measurement of weight during subsequent patient follow-ups is needed so that it could offer the possibility to detect weight variation after treatment which could also act as an indicator for prognostic outcomes.

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DISCLOSURE STATEMENT

No conflict of interest exists, and the manuscript is approved by all authors for publication.

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