

RESEARCH ARTICLE

Adherence to Capecitabine Treatment and Contributing Factors among Cancer Patients in Malaysia

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Abstract

Ensuring adherence to chemotherapy is important to prevent disease progression, prolong survival and sustain good quality of life. Capecitabine is a complex chemotherapeutic agent with many side effects that might affect patient adherence to treatment. This cross sectional study aimed to determine adherence to capecitabine and its contributing factors among cancer outpatients in Malaysia. One hundred and thirteen patients on single regime capecitabine were recruited from Hospital Sultan Ismail and Hospital Kuala Lumpur from October 2013 to March 2014. Adherence was determined based on adherence score using validated Medication Compliance Questionnaire. Patient socio-demographics, disease, and treatment characteristics were obtained from medical records. Satisfaction score was measured using the validated Patient Satisfaction with Healthcare questionnaire. The mean adherence score was 96.1% (standard deviation: 3.29%). The significant contributing factors of adherence to capecitabine were Malay ethnicity [$\beta=1.3$; 95% confidence interval (CI): 0.21, 2.43; p value=0.020], being female [$\beta=1.8$; 95% CI: 0.61, 2.99; p value=0.003], satisfaction score [$\beta=0.08$; 95% CI: 0.06, 1.46; p value=0.035], presence of nausea or vomiting [$\beta=2.3$; 95% CI: 1.12, 3.48; p value <0.001] and other side effects [$\beta=1.45$; 95% CI: 0.24, 2.65; p value=0.019]. Adherence to capecitabine was generally high in our local population. Attention should be given to non-Malay males and patients having nausea, vomiting or other side effects. Sufficient information, proactive assessment and appropriate management of side effects would improve patient satisfaction and thus create motivation to adhere to treatment plans.

Keywords: Adherence - capecitabine - oral chemotherapy - ethnicity - gender - Malaysia

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Introduction

Cancer is one of the major causes of morbidity and mortality in the world. According to the World Health Organization in 2008, approximately 7.6 million people died of cancer which accounted for 13% of total deaths worldwide (WHO, 2013). Although the number of new cancer cases seems to decrease (Omar et al., 2006; Omar and Tamin, 2007), probability that a Malaysian will get cancer in his/her lifetime is still high which is 1 in 4 (Lim et al., 2002). Breast and colorectal cancer have been reported as the two most frequent cancers among Malaysian population followed by lung, nasopharynx, cervix, lymphoma, leukaemia, ovary, stomach and liver cancer (Omar and Tamin, 2007).

Surgical intervention has been considered as the primary treatment of cancer; however, the use of chemotherapy has expanded over the last decades especially for their role as adjuvant therapy. Over the last decades, oral chemotherapy has been chosen over

conventional parenteral chemotherapy in cases whereby patients' convenience and improved quality of life were emphasized. Some of the oral chemotherapy has shown comparable survival outcomes compared to parenteral therapy. Capecitabine, for instance, is an oral fluoropyrimidine that has been shown to be effective against colorectal cancer with disease-free survival equivalent to that of fluorouracil-plus-leucovorin treatment (Twelves et al., 2005).

In addition to frequently associated with inconvenience, pain and discomfort due to venopuncture and risk of extravasation, parenteral chemotherapy was also associated with significant psychological distress, prolonged hospital stays and financial burden (Payne, 1992). Home-based treatment with oral chemotherapy requires self-medication with less frequent visits to the oncologist compared to parenteral chemotherapy which limits educational and monitoring opportunities (Staddon, 2011). Challenges in adhering to oral chemotherapy may be different from other medications for chronic diseases due

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to the complexity of certain oral chemotherapy regimens. Some oral chemotherapy such as capecitabine and lapatinib often associated with complex cyclic schedules, drug-free period and more adverse events (Spoelstra and Given, 2011). Due to these challenges, patients with poor adherence may not receive the full benefit of treatment and may consequently experience suboptimal outcomes, poor survival rates, potential adverse events and increase cost burden related to hospitalization (Ruddy et al., 2009). A large Australian and New Zealand data reported that 3.4% women with early invasive breast cancer declined clinicians' treatment recommendations and 23.6% of them declined chemotherapy (Roder et al., 2012).

Capecitabine, an oral cytotoxic agent has shorter elimination half-life from 0.49 to 0.89 hours (Walko and Lindley, 2005) whereby, the adherence issue might give more impact on its antitumor effect. Administration of capecitabine requires a complex instruction on its administration which is twice daily dosing, within 30 minutes after food, 12-hours apart and more complex cyclic dosing schedule of 21 days with 7 days drug-free period. Capecitabine also associated with high occurrence of adverse events similar to 5-fluorouracil (5-FU) such as diarrhoea (55%) and hand-foot syndrome (54%) that may contribute to poor compliance (Roche, 2014). Being relatively more expensive than other commonly available oral cytotoxic drugs in local government hospital settings, knowing the estimated level of adherence with this drug can help the clinicians and the pharmacists to properly manage those patients with poor adherence to ensure cost-effective therapy with capecitabine.

While adherence to prescribed medication has been studied extensively in many chronic diseases and from different age aspect among both pediatric and elderly patients (Cramer, 1998), studies on oral chemotherapy are still lacking. Adherence to medication was defined synonymously with compliance, as the degree or extent of conformity to provider's recommendation with respect to the timing, dosage and frequency (Cramer et al., 2008). In other point of view, the extent to which a patient's behavior concurs with medical advices is also defined as compliance (Dusing, 2001). Since the health-related quality of life aspect has been increasingly emphasized by the physicians in cancer management (Stiggelbout and De Haes, 2001), optimal medication adherence among these patients should also be achieved to further improve the quality of life of the patients as in reducing clinical symptoms (due to suboptimal outcome and disease progression) and avoiding side effects.

In cancer management, there is no consensus or agreement concerning a definition of "adequate adherence". Previous researchers have been using ranges from 80% to 95% depends on type of diseases and drugs that being studied (Ruddy et al., 2009). Two other similar studies set even higher cut-off point for adherence to capecitabine which is not less than 100% (Winterhalder et al., 2011; Bhattacharya et al., 2012), since they considered that significant deviation from the actual standard may result in significant effect on efficacy. Meanwhile, two other studies set 80% and above as being adherent (Partridge et al., 2010; Thivat et al., 2013).

Understanding the contributing factors to adherence is hoped to eliminate the barriers to adherence, consequently ensuring the patients to get full benefit from their medications. Generally, the World Health Organization Adherence Model (Sabate, 2003) suggested that there are five dimensions or categories of factors influencing medication adherence which are patient-related factors, treatment-related factors, disease-related factors, healthcare system-related factors and socioeconomic factors.

Patient-related factors or patient barriers include self-efficacy, forgetting their medications, patients beliefs and knowledge about their diseases and medications, use of complimentary medicines, patients attitude, expectations about consequences to non-adherence, and awareness of adherence aids (AlGhurair et al., 2012). Most of these domains are usually covered under the assessment of medication-taking behaviour and medication-stopping behaviour, evaluated in most of validated self-report questionnaires (Hassan et al., 2006). The association between complimentary medicines and adherence has been studied in other chronic diseases but not specifically among cancer patients.

As for socioeconomic-related factors, social support is the factor that often being studied and has shown significant association with adherence in a few studies. DiMatteo (2004) found that patients with good social support from cohesive family were significantly 1.74 more adherent to their medications compared to the other counterparts. There was also a modest increase of adherence in married patients or those living with another adult.

Disease-related factors or condition barriers are represented by domains that are usually linked to the cognitive function, patient presenting illness and the underlying diseases that may influence their level of adherence, which can also be represented by age factor, type of disease and other comorbidities respectively.

Treatment-related factors are well-recognized factors to non-adherence to oral chemotherapy (Verbrugghe et al., 2013). Occurrence of medication inconvenience and side effects have been widely studied as the contributing factors to adherence and the result was frequently found to be significant regardless of any type of chronic diseases (Hassan et al., 2006; Spoelstra and Given, 2011; AlGhurair et al., 2012; Ahmad et al., 2013; Verbrugghe et al., 2013).

As for side effects, a study conducted on 177 cancer patients in Switzerland highlighted that there was a trend towards better adherence among patients with lesser side effects (Winterhalder et al., 2011). Nonetheless, Bhattacharya and colleagues found that the number of side effects did not influence patients' adherence to their medication (Bhattacharya et al., 2012).

Satisfaction and perception with healthcare providers is one of the commonly studied healthcare system-related factors. In a study conducted among hypertensive patients in a teaching hospital in Kelantan, poor overall patient satisfaction was found to significantly reduce the level of adherence by three-percent odds (Hassan et al., 2006).

Although previous study findings have shed some light

on the potential factors of non-adherence among cancer patients, limited sample size, univariable analysis with lack of confounder control and low generalizability due to restricted study population require more similar studies on the same issues to be conducted.

This study aims to determine the level of adherence to capecitabine and its contributing factors such as socio-demographic characteristics, disease-related, treatment-related and healthcare system-related factors among cancer outpatients in Malaysia.

Materials and Methods

This study was a multi-centred, cross sectional study conducted from October 2013 to February 2014. Two outpatient oncology pharmacy units in two referral oncology in South and Central region of Peninsular Malaysia hospitals namely Hospital Sultan Ismail, Johor Bahru and Hospital Kuala Lumpur, Malaysia were involved. Study respondents included adults diagnosed with any type of cancer based on clinical symptoms, biopsy and radiological imaging and relevant blood tests. Eligible cancer patients attended the oncology clinics for regular follow up and were prescribed with capecitabine as a single regimen. Subjects were selected if they had been on capecitabine treatment for at least one cycle. Meanwhile, patients below 18 years old, too ill to be interviewed or unable to respond to the questions or could not speak and understand Malay and English language were considered ineligible to participate.

Data was collected upon patients visit to the pharmacy to collect their medication. Eligible patients were identified and invited to participate in the study. The study participants were then required to fill up the informed consent form prior to answering the questionnaires. This study was reviewed and approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia and the Human Research Ethics Committee, Universiti Sains Malaysia (USM).

Data on the adherence to capecitabine was collected using a self-reported questionnaire called Medication Compliance Questionnaire (MCQ) (Hassan et al., 2006). Data on contributing factors was collected mainly from medical records except for socio-demographic characteristics, and healthcare-system related factors; self-reported questionnaires (MCQ) and Patient Satisfaction with Healthcare Questionnaire (PSHC). Patient medical records were used to collect data on treatment-related and disease-related factors and were obtained from Medical Record Department in both study locations. Data collection form was used to guide and to ensure the completeness of data collection throughout the study. The questionnaires used in this study were guided self-administered questionnaires. All the study participants were guided to answer and the researcher was present to assist with answering the questionnaire whenever required. Only one researcher involved with data collection to ensure the uniformity of the information given.

MCQ contains 10 items with five-point Likert-type response format with two domains measuring specific medication-taking and medication-stopping behaviour.

All negatively worded scores were reversed and all scores were converted to a 0 to 100 scale. It had been validated with internal consistency of Cronbach's $\alpha = 0.67$ and 0.84 for respective domains, with test-retest single measure intraclass correlation coefficients (ICC) were 0.78 and 0.93 (Hassan et al, 2006). PSHC comprises of four domains, consists of overall patient satisfaction, satisfaction with appointment satisfaction with doctors service and satisfaction with pharmacy services. It uses 5-point Likert scale from 1 (very dissatisfied) to 5 (very satisfied). The internal consistencies reliabilities ranged from 0.76 (satisfaction with appointment) to 0.91 (satisfaction with pharmacy), and test-retest single measure ICC ranged from 0.54 (satisfaction with appointment) to 0.70 (satisfaction with pharmacy). All negatively worded scores were reversed and all scores were converted to a 0 to 100 scale. Higher score indicates greater satisfaction (Hassan et al, 2006). Similar content and face validity with MCQ were conducted and its use among cancer patients was approved.

Statistical analysis

Adherence score was the main outcome in this study and measured in mean percentage score and its standard deviation (SD). Four contributing factors to adherence consisted of socio-demographic characteristics, disease-related, treatment-related and healthcare-related factors. The selection of significant variables to be included in the general linear regression model was based on the results from the simple linear regression analysis. Automated variable selection method was used to obtain a preliminary main effect model. The fit of the model was examined based on the fulfilment of regression assumptions. The final results were presented in adjusted regression coefficient with 95% confidence interval and p value. The p value of less than 0.05 was considered as statistically significant. Analyses were performed using STATA SE version 11.

Results

A total of 130 out-patients cancer on oral capecitabine who came for follow up in Oncology Clinic and collected their medications in the pharmacy were identified and consented to participate in the study. Further data

Table 1. Socio-Demographic Characteristics of Cancer Patients on Capecitabine (n=113)

Variables	n (%)
Age (mean, SD)	58.3 (11.35)
Gender	Female 71 (62.80) Male 42 (37.20)
Race	Malay 57 (50.40) Chinese 52 (46.00) Indian 4 (3.50)
Marital status	Married 85 (75.20) Single/ separated 28 (24.80)
Use of complimentary medicines	Yes 44 (38.90) No 69 (61.10)
Centre	HSIJB 42 (37.20) HKL 71 (62.80)

*HSIJB (Hospital Sultan Ismail, Johor Bahru), HKL (Hospital Kuala Lumpur)

investigation from medical record review excluded 17 participants who were not on standard capecitabine regime such as continuous regime (ECX regime) and concurrent chemotherapy radiotherapy (CCRT). Ultimately, only a total of 113 study participants were included in the study

Table 2. Disease-related Characteristics of Cancer Patients on Capecitabine (n=113)

Variables		n (%)
Cancer type	Colorectal	60 (53.1)
	Breast	40 (35.4)
	Others	13 (11.5)
Cancer staging	Stage I	1 (0.9)
	Stage II	12 (10.6)
	Stage III	16 (14.2)
	Stage IV	84 (74.3)
Comorbidities	Yes	58 (51.3)
	No	55 (48.7)
Pre chemo ECOG Performance status	0	33 (29.2)
	1	54 (47.8)
	2	22 (19.5)
	3	4 (3.5)

Table 3. Treatment-Related and Healthcare-Related Characteristics of Cancer Patients on Capecitabine (n=113)

Variables		n (%)
No. of concomitant oral drugs (median, IQR)		0 (2)
Current cycle (median, IQR)		2 (4)
Total daily dose of capecitabine (mg) (mean, SD)		2820 (639)
Pill burden	500mg	94 (83.2)
	500&150 mg	19 (16.8)
Presence of diarrhea	Yes	21 (18.6)
	No	92 (81.4)
Presence of nausea/vomiting	Yes	39 (34.5)
	No	74 (65.5)
Presence of stomatitis	Yes	35 (31.0)
	No	78 (69.0)
Presence of hand-foot syndrome (HFS)	Yes	74 (65.5)
	No	39 (34.5)
Presence of other side effects	Yes	35 (31.0)
	No	78 (69.0)
Grading of HFS	No HFS	40 (35.4)
	Grade I	55 (48.7)
	Grade II	15 (13.3)
	Grade III	3 (2.7)
Satisfaction score (mean, SD)		82.3 (7.9)

consisted of 41 patients from Hospital Sultan Ismail and 71 patients from Hospital Kuala Lumpur (Table 5.1). Descriptive statistics of the study respondents based on socio demographic characteristics, disease-related factor, treatment-related factor and healthcare system-related factors were shown in Table 1, 2 and 3 respectively. Adherence score, ranged from 87.3% to 100% with most of the participants were highly adhered to oral capecitabine. The mean adherence score was 96.1% (SD: 3.29%).

The results from general linear regression analysis shown in Table 4 indicated that race, gender, presence of nausea and vomiting and other side effects, and satisfaction score were the associated factors of adherence to capecitabine. The adherence score of Malay cancer patients were significantly higher than non-Malay patients by 1.3% (95%CI:-2.43,0.21; p=0.020). Whereas, the adherence score of female cancer patients were significantly higher than male cancer patients by 1.8% (95%CI: 2.99, 0.61%; p=0.003). There was a significant linear relationship between presence of nausea and vomiting among cancer patients and adherence score (p value < 0.001). Cancer patients who did not have nausea and vomiting during oral capecitabine treatment had 2.3% higher adherence score compared to cancer patients who experienced nausea and vomiting (95%CI: 1.12, 3.48%). Meanwhile, cancer patients who did not experience other side effects during oral capecitabine treatment had 1.45% higher adherence score compared to cancer patients who experienced other side effects (95%CI: 0.24, 2.65%; p=0.019). Satisfaction score also showed significant linear relationship between satisfaction score and adherence score among cancer patients (p value = 0.035). Every 10% increase in satisfaction score resulted in 0.8% increase in adherence score among patients on oral capecitabine (95%CI: 0.05, 1.46%). The model sufficiently fit well. Model assumption of independent samples were fulfilled, overall linearity assumption was met, there was no heteroscedasticity found, the distribution of residuals were sufficiently normal, fit of numerical independent variable was not violated and no significant interaction among independent variables was detected.

Discussion

Similar to previous studies regarding adherence to oral

Table 4. Factors Associated with Adherence Score among Cancer Patients on Oral Capecitabine (n=113)

Variables		Simple Linear Regression			Multiple Linear Regression ^a		
		Crude regression coefficient (b)	95% CI	p value	Adjusted regression coefficient (b)	95% CI	p value
Gender	Male	-	-	-	-	-	-
	Female	-1.02	-2.28, 0.25	0.113	1.8	0.61, 2.99	0.003
Race	Non-Malay	-	-	-	-	-	-
	Malay	-1.25	-2.46, 0.04	0.04	1.32	0.21, 2.43	0.020
Presence of nausea and vomiting	Yes	-	-	-	-	-	-
	No	2.07	0.84, 3.31	0.001	2.3	1.12, 3.48	<0.001
Presence of other side effects	Yes	-	-	-	-	-	-
	No	1.41	0.10, 2.72	0.035	1.45	0.24, 2.65	0.019
Satisfaction score		0.09	0.01, 0.16	0.022	0.08	0.01, 0.15	0.035

^aa Coefficient of determination, R²=0.26

anticancer drugs, this study contributed another finding to support that cancer patients are generally more adhered to their oral chemotherapeutic treatment compared to patients with other chronic diseases. The distribution of adherence score in this study was slightly skewed to the left but sufficiently normal indicating that more patients achieved high adherence score with three quarter of the participants scored more than 90% (median 96.4%; IQR: 3.69). In spite of using different measurement tool for the outcome, these results were very similar with a study done by Krolop et al. (2013). Other previous studies that divided adherence into binary outcome (adherent vs non adherent) also highlighted that the proportion of patients that fully adhered to oral capecitabine was mostly greater than 90% (Winterhalder et al., 2011; Thivat et al., 2013). Although cancer patients are highly motivated due to the seriousness and poor prognosis of their disease, discouragement may also occur that may ultimately result in poor adherence to their treatment.

Study results have shown that gender and race are linked to adherence to oral capecitabine. In view of gender, male cancer patients had lower adherence score compared their female counterparts. The connection between gender and adherence has frequently found inconsistent in many adherence studies and if the significant association existed, it may actually reflect the social situation of the studied population. For example, female patients are tied with responsibility of managing their families and households, thus they have greater concern about their health so that they can continuously serve their families in spite of their disease.

Another socio demographic characteristic that reflects social situation of the population is marital status. Previous meta-analysis of 122 studies found that married patients with high emotional well-being were almost two times more adhered to their medication compared to single and unmarried patients (DiMatteo, 2004). In this study, it appeared that the association of marital status with adherence existed among cancer patients but it was not significantly meaningful.

Malay cancer patients were found to be more adhered to oral capecitabine compared to non-Malay patients whereby 92.9% of them were Chinese. This result was contrary with two previous local studies done among hypertensive and diabetic patients (Hassan et al., 2006; Ramli et al., 2012) although only latter study showed significant association. However, unlike other drugs for chronic diseases, capecitabine is often recognized as the oral drug with complex regimen due to the complexity in administration of the drug (Spoelstra and Given, 2011) thus sufficient information on treatment is strictly required. Even though each of the patients was provided with individual capecitabine treatment handbook in their preferred language, communication barrier cannot be ruled out. Adequate and clear information should be given upon drug dispensing especially in patients' respective language to avoid misinterpretation of information.

Age was normally distributed with the mean age of 58.3 years old (SD: 11.35) indicating that prescribing of oral capecitabine is not specifically dedicated to older patients. It was a commonly held view that younger age

is more associated with adherence (Hassan et al., 2006; Verbrugghe et al., 2013). This study also showed the same negative correlation between age and adherence score but not significantly proven.

Four possible disease-related factors including cancer type, cancer stage, comorbidities and ECOG Performance status were evaluated for their association with adherence score. This study shows that colorectal and breast carcinomas were the type of cancers whereby oral capecitabine was highly prescribed, consistent with the Ministry of Health Drug Formulary 2012 which stated that the approved indication for oral capecitabine is as the first line treatment for metastatic colorectal, breasts and gastric carcinoma as well as stage III colorectal carcinoma. Gastric (3 patients), liver (3 patients) and nasopharyngeal carcinoma (7 patients) contributed to only 11.5% (n = 13) from the total usage of oral capecitabine in this study. Oral capecitabine is a second line treatment option for recurrent and metastatic nasopharyngeal and liver carcinoma whereby in Malaysia, it is an off label indication. Although this study shown that cancer type was not contributed to adherence score, univariable analysis showed that some patients with other cancer types had lower adherence score compared to patients with colorectal carcinoma (95%CI: -2.9, 1.05%). Although insignificant, this factor cannot be overlooked since patients with nasopharyngeal carcinoma usually presented with difficulty in swallowing. Larger group of patients with other types of cancer should be involved in the future to give more reliable information about this association. Cancer stage as well did not show any association with adherence score and this is supported by several previous studies (Partridge et al., 2010; Thivat et al., 2013; Verbrugghe et al., 2013).

No association between multiple chronic diseases and adherence was established in this study. This finding is contrary with previous studies whereby underlying diseases were often found to be inversely correlated with adherence in previous studies (Ahmad et al., 2013; Verbrugghe et al., 2013). Comorbid patients are usually related to multiple drug use, elevated anxiety and depression due to the presence of underlying disease that may be the reasons of being non-adherent. However among cancer patients, they may have varied opinion and concern about their health outcomes particularly in obtaining longer survival.

ECOG Performance status is another relevant issue evaluated in the study. Disease progression and its influence on the daily living activities of the patients might also contribute to their adherence to cancer treatment. This study yielded similar result with the earlier two studies on adherence to oral capecitabine (Winterhalder et al., 2011; Thivat et al., 2013) by which adherence was not affected by the patients' ECOG performance status. Intriguingly, univariable analysis discovered that patients with ECOG performance status of 3 had relatively positive but insignificant correlation with adherence score compared to ECOG performance status of 2 and 1 (b= 1.53, 95%CI: -1.95, 5.01%) and this was in line with findings from Winterhalder et al. (2011). It is possible to postulate that patients with higher ECOG status had assured adherence to treatment with help of their caretakers.

Treatment-related side effects were the most frequently reported factor contributing to non-adherence to oral capecitabine. The occurrence of side effects mainly diarrhea, nausea and vomiting, stomatitis and hand-foot syndrome was common among patients on oral capecitabine treatment, and very likely to affect the patients' quality of life. Bhattacharya et al. (2012) in her study reported that a majority of 80% of the patients actually experienced side effects and the most troubling side effects were hand-foot syndrome and fatigue. In this study, presence of nausea and vomiting and other side effects had significantly affected adherence to oral capecitabine. Nausea and vomiting often related to reduced appetite and indirectly resulted in poor acceptable to medications. Other side effects particularly fatigue, dizziness and headache were commonly reported in this study and often lead to patients' discouragement to persist with their treatment.

Generally, treatment inconvenience has been associated with non-adherence in many studies involving both cancer and non-cancer population (Atkins and Fallowfield, 2006; Hassan et al., 2006; Ramli et al., 2012). Other than side effects, treatment inconvenience that includes difficulties in swallowing tablets and complexity of regimen is another obstacle for adherence. Complexity of regimen with oral capecitabine is justified as patients on standard oral capecitabine regimen alone are required to take up to four sizeable tablets of 500mg every 12 hours 30 minutes before food. Patients must also stick to the dosing schedule for 14 days and rest for 7 days before came to the subsequent follow up for review. In relation to this issue, the increased number of concomitant oral drugs, pill burden as in different strength of capecitabine tablets, and total dose of capecitabine were the responsible factors to indicate complexity of regimen in this study.

The number of concomitant drugs taken has shown to be strongly correlated with adherence in previous study (Ramli et al., 2012; Verbrugghe et al., 2013). However, it was not stated which type of drugs have been considered as the concomitant drugs whether it also included injectable drugs or short terms drugs such as antibiotics. By taking into account only oral drugs for chronic diseases, this study, however found that there was so association between numbers of concurrent oral drugs with adherence score. It needs to be stated that the distribution of concomitant drugs in the study population was positively skewed with half of the patients were not on other chronic diseases treatment at all. For pill burden factor, taking additional 150mg strength tablet together with 500mg strength tablet did not significantly change the adherence score. The total daily dose of capecitabine was analysed and it turned out that the effect towards adherence score was also insignificant. Considering the total number of capecitabine tablets taken per dose may yield different result however that parameter was not included in the analysis.

Other treatment-related factors such as the number of current cycle, treatment intent and the use of complementary medicine were not significantly related to adherence according to this study. Parallel with earlier studies among capecitabine patients, patient adherence did

not seem to be affected by the number of cycle (Partridge et al., 2010; Krolop et al., 2013; Thivat et al., 2013).

It was hypothesised that patients who seek for complementary medicines would appear to be less adhered to their treatment, however, the relationship with medication adherence among local cancer patients has not been published before and the scope should be narrowed down to more specific type of complementary medicines.

Confronting a serious life threatening disease and dealing with psychological stress once diagnosed with cancer necessitate these patients to have a good practical, informational and warm support especially from the healthcare providers. Sufficient support will allow these patients to cope with their disease and adhere to the treatment plan well so that the treatment outcome can be achieved. Satisfaction with healthcare providers has shown a significantly positive correlation with adherence in this study and this finding is in line with previous studies done among both cancer and non-cancer patients (Hassan et al., 2006; Bhattacharya et al., 2012). Although there was a significant correlation, the increment of adherence score with every increase of 10% satisfaction score was rather small which was only 0.8%.

PSHC questionnaire evaluates satisfaction based on several domains including overall satisfaction, satisfaction with appointment, satisfaction with doctors and satisfaction with pharmacy services. Instead of looking at the satisfaction score as a whole, studying each domain separately might give clearer picture about the important domains that actually contributed to adherence among cancer patients. Nonetheless, during the interview, patients often claimed that they either received contradicting information or not given sufficient information about oral capecitabine.

Limitation of the study, there are several limitations encountered in this study. Prospective cohort using repeated measurement analysis might be the best option to conduct this study. However, due to time constraint, cross sectional design was chosen instead. Moreover, direct measurement tool such as blood levels assessment and MEMS would provide more reliable information for repeated measurement compared to self-report tools which was frequently associated with overestimation (Ruddy et al., 2009).

In this study, adherence to oral capecitabine was assessed using MCQ, a validated self-report questionnaire which was previously used among hypertensive patients. Although construct validity of the questionnaire for use among cancer patients was not established, this questionnaire had been reviewed by the oncology team represented by an oncology consultant and three oncology pharmacist in Hospital Sultan Ismail for face and content validity. MCQ was found suitable for use among cancer patients.

Since the use of MEMS was costly and not practical in this study, combination of several methods such as pill counts and medication diary might give more reliable information compared to questionnaire alone. However, for oral capecitabine, pill count could not tell whether the patient took their medication during the 14-days period or during drug-free period to replace the skipped doses.

Medical diary appears to be the best option yet, with our local culture, it was not easy to train the patients to fill up the diary accordingly and most of them were not aware to bring along their diary for assessment.

In view of statistical analysis, since there is no consensus on cut-off point to define adequate adherence with oral chemotherapy, multiple linear regression model which analyse the outcome based on the actual score was applied to minimize arguments about the most preferable cut-off point to be used. Yet, different self-report tools might also lead to different interpretation of the study findings.

Although adequate sample size was achieved, unequal subgroup distribution was noticeable in some categorical variables including race, cancer type, cancer stage and ECOG performance status. This subgroup imbalance resulted in re-categorization thus complicated the variables interpretation if the association with the outcome really existed. Some numerical independent variables were also found to be skewed, for example, number of current cycle and number of concomitant oral drugs. Expanding the sample size or stratified sampling based on important subgroups might be necessary in the future to overcome this issue.

All the explanatory variables explored in this study could only explain 25.8% of variation in the adherence score. Gender, race, satisfaction score and presence of side effects during capecitabine treatment were not the only predictors of adherence to oral capecitabine. Patient-related aspect, for instance, was one of the factors that were not widely explored in this study. WHO Multidimensional Adherence model described patient-related barriers as pertaining to patients belief, attitude and perception towards medicines (AlGhurair et al., 2012). By focusing on these domains in future studies, attention could be given more towards improving patients' belief and attitude in medication taking. Factors such as social support, cultural and language barriers and logistic problem might also contribute to better adherence to oral chemotherapy.

In conclusion, the mean adherence score of the study population was 96.09% (SD: 3.29) that range from 87.3% to 100%. Factors contributed to the adherence score of these patients including gender, race, satisfaction score and the presence of nausea, vomiting and other side effects during capecitabine treatment.

Symptoms of presenting side effects should be assessed and treated accordingly during their visit to oncology clinic for review. Nausea and lethargic often caused these patients to lose their appetite and created a sense of inconvenience when taking their medications. Pharmacists should play their active roles by also reviewing the encountered side effects while dispensing and communicate with the doctors when necessary. Previously, presence of diarrhoea and hand-foot syndrome, which were potentially severe side effects, had been routinely reviewed and treated during their visit and the patients seemed to cope well with these side effects with no needs for dose adjustment.

Satisfaction towards healthcare system is another issue that should be improved. Miscommunication and lack

of information often found to be related with adherence among cancer patients especially with oral capecitabine. Sufficient and clear information about disease progression and treatment plan would create a sense of comfort for the patients and further motivate them to adhere to their treatment plans. Miscommunication when obtaining blood test results was one of the reasons the patient delayed their treatment and this problems should be appropriately solved in the departmental level. Patients' regular visits to the pharmacy to collect medication sometimes were taken for granted by the pharmacists. Pharmacist at the dispensing counter should be more tactful and proactive by reviewing any medication-related problems or misleading information when there is an opportunity to do so.

Communication and cultural barrier is another potential issue related to race factor that might contributed to low adherence. When there is a necessity and if it is appropriate, first medication counselling should be given in the patients' first language.

Last but not least, recruiting more patients by expanding the study duration and involving more oncology referral hospitals would be able to provide more reliable information regarding this issue. Construct validation of the MCQ should also be established among cancer patients so that it can be used as a standard questionnaire in measuring adherence of oral chemotherapy in the future.

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