

Effects of Complementary and Alternative Medicine on Chemotherapy Delivery in Thai Patients

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Abstract

Background: Complementary and Alternative Medicine (CAM) is widely used among cancer patients worldwide. This prospective observational study aimed to show the effect of CAM use on chemotherapy delivery in Thai patients. **Methods:** During March 2014 to February 2015, the patients with breast, lung or colorectal cancer receiving first cycle chemotherapy at King Chulalongkorn Memorial Hospital were enrolled. The correlation between CAM using and chemotherapy schedule delay and dose reduction, dose intensity, quality of life and adverse event rates were analyzed. **Results:** There were 80 (44.20%) patients using CAM among 181 enrolled patients. Seventy six CAM users and 97 non-CAM users receiving 2nd cycle of chemotherapy were included for primary analysis. The chemotherapy schedules were delayed and/or reduced in 40 (52.6%) and 48 (49.5%) in CAM users and non-CAM users, respectively, $p=0.681$. The mean relative dose intensity (RDI) were 92.4% and 94.1% in CAM and non-CAM users, respectively, $p=0.244$. However, there were significantly more CAM users receiving chemotherapy less than 90% RDI (34.8% vs 19.8%, $p=0.033$). As compared to first cycle, at third cycle, the mean QOL score changes were -4.63 (95% CI -2.49-9.27) and -8.02 (-2.36- 9.142) in CAM user and non-CAM user, respectively ($p=0.255$). There were significantly higher rates of grade 3 or 4 anemia (5.1% vs 0%, $p=0.024$), and grade 2 malaise (19.0% vs 5.1%, $p=0.004$) in CAM users. **Conclusions:** There were similar overall rates of chemotherapy schedule delay and dose reduction between CAM- and non-CAM users. However, there were less CAM-users achieving 90% chemotherapy RDI.

Keywords: Complementary and Alternative Medicine (CAM)- cancer- chemotherapy

Asian Pac J Cancer Prev, 22 (12), 3977- 3983

Introduction

Complementary and Alternative Medicine (CAM) is a medical product or practice that is used together with or instead of standard medical care. It is widely used among cancer patients worldwide, ranging from 30-60% (Shih et al., 2009; Akyol and Oz, 2011; Naing et al., 2011; Horneber et al., 2012; Klafke et al., 2012; Puataweepong et al., 2012; Oyunchimeg et al., 2017; Jones et al., 2019; Sanford et al., 2019; Wode et al., 2019; Razali, 2020). In Thailand, one study reported CAM use in 60.9% of cancer patients. The major reasons for CAM use in cancer patients are to improve wellbeing and immunity, relief conventional treatment toxicity and treat cancer (Shih et al., 2009; Puataweepong et al., 2012; Smith et al., 2014; Oyunchimeg et al., 2017; Razali, 2020). However, most reports demonstrated patient satisfaction and benefit of CAM in term of quality of life and spiritual well-being improvement (Chandwani et al., 2010; Mao et al., 2010;

Wode et al., 2019).

Up to 70% of patients reported on CAM use along with cancer treatment (Puataweepong et al., 2012; Zeller et al., 2013; Drozdoff et al., 2019; Razali, 2020). Although there were inadequate evidence supporting the benefits of CAMs, it was widely believed to have no harm. However, there were some reports of potential harms of CAMs. Several herbal medicines are composed of biologically active compounds causing drug interaction to chemotherapy (Zeller et al., 2013; Wanwimolruk et al., 2014; Wanwimolruk and Prachayasittikul, 2014; Drozdoff et al., 2019; Jermini et al., 2019). Some herbal medicines had risks to develop hepatotoxicity and renal toxicity (Teo et al., 2016; Yang et al., 2018; Philips et al., 2019). Moreover, since there are various sources of herbal products and quality controls of production, contamination causing serious adverse events is another concern for CAM use (Posadzki et al., 2013).

CAM use during chemotherapy is not uncommon

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(Zeller et al., 2013; Drozdoff et al., 2019). Although many patients expect to improve chemotherapy tolerability and treatment outcomes by using CAM, the potential harm of CAMs might preclude these expected benefit. Although, some studies showed protective effects of CAMs for chemotherapy induced leucopenia, they did not demonstrate how CAMs affect chemotherapy delivery (Zhuang et al., 2009; Zhuang et al., 2012; Jia et al., 2015). We conducted this prospective observational study to explore the effect of CAM on chemotherapy treatment delivery in Thai cancer patients receiving chemotherapy.

Materials and Methods

Patients

The patients with breast, lung or colorectal cancer receiving first cycle of standard dose adriamycin plus cyclophosphamide, carboplatin plus paclitaxel or gemcitabine and capecitabine plus oxaliplatin regimens, respectively, at the King Chulalongkorn Memorial Hospital (KCMH) were enrolled. All patients provided written informed consent before being enrolled to the study.

We conducted the face-to-face interviews for each patient to collect the CAM use data. The interviewers were the trained health care personnel not-involving in patient cancer treatments. After an eligible patient providing the informed consent, two interviews were done on the day patient receiving first and third cycles of chemotherapy. The data was reported only to investigator after completion of all treatment sessions in all patients. We assessed the quality of life by using FACT-G (Functional Assessment of Cancer Therapy – General) permitted by FACIT.org. The chemotherapy schedule and dose modifications, and adverse events were collected from medical records by investigators. The chemotherapy schedule delays and dose reductions were assessed in second and third chemotherapy cycles. Chemotherapy delay was defined of any postpone of chemotherapy planned schedule and dose reduction was defined as any dose reduction in subsequent cycle from actual dose in first cycle. We

calculated chemotherapy dose intensity in all patients receiving 4 cycles of chemotherapy. Dose intensity is unit dose of chemotherapy administered per unit time. Relative dose intensity (RDI) was defined as actual dose divided by the standard dose.

The definition of Complementary and Alternative Medicine (CAM) in this study was any medical product that patient put into body per oral, per intravenous injection or per rectal on purpose for treatment, that is not thought of as standard care. The severity of adverse events was assessed based on the Common Terminology Criteria for Adverse Events, version 3.0.

Statistical Analysis

The co-primary end points were the rates of schedule delay and/or dose reduction, and dose intensity of chemotherapy. All primary endpoints were assessed based on chemotherapy delivery in first three cycles. According to our chemotherapy administration database, the rates of chemotherapy schedule delay and/or dose reduction was around 30%. The 25% of difference in chemotherapy delay and/or reduction rates between CAM and non-CAM users were considered clinical significance. With 80% power to detect that difference, we required 93 patients for each group. We compared the rates of chemotherapy schedule delay and dose reduction, rates of RDI less than 90% and adverse event rates between CAM users and non-CAM users by Chi-squared test. 95% confidence intervals for the chemotherapy delivery outcomes were calculated by bootstrap method. We used t-test to compare chemotherapy dose intensity between CAM users and non-CAM users. P values <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 16.0 for Windows software (SPSS Inc., Chicago, IL).

Results

Between March 2014 and February 2015, 181 patients were enrolled into study. Half of patients (55.2%) were patients with breast cancer receiving adriamycin and

Table 1. Baseline Characteristics Stratified According to CAM Using

Characteristics	Total (N=181)	CAM users (N=80)	Non-CAM users (N=101)	p-value
Gender				
Male	43 (23.8%)	23 (28.8%)	20 (19.8%)	0.16
Female	138 (76.2%)	57 (71.3%)	81 (80.2%)	
Age				
Mean	54.26	55.28	53.46	0.461
Range	28 – 80	29 – 80	28 – 80	
Cancer type				
Breast	100 (55.2%)	39 (48.8%)	61 (60.4%)	0.118
Others	81 (44.8%)	41 (51.3%)	40 (39.6%)	
Regimens				
Adriamycin/Cyclophosphamide	100 (55.2%)	39 (48.8%)	61 (60.4%)	0.094
Carboplatin/Paclitaxel	17 (9.4%)	5 (6.3%)	12 (11.9%)	
Carboplatin/Gemcitabine	29 (16.0%)	16 (20.0%)	13 (12.9%)	
Capecitabine/oxaliplatin	35 (19.3%)	20 (25.0%)	15 (14.9%)	

Table 2. CAM Use Detail

N=80	Number (%)
Reason for CAM use	
To improve efficacy of conventional therapy	21 (26.3)
To decrease toxicity from the convention therapy	5 (6.3)
To decrease worry and fear from the convention therapy	19 (24.4)
To gain hope, belief and faith in convention therapy	6 (7.5)
To treat cancer	5 (6.3)
Others	6 (7.5)
Type of CAM	
Herbal medicine	52 (65.0)
Nutritional therapeutics	23 (28.8)
Other	5 (6.3)
Satisfaction	
Satisfy	38 (47.5)
Neutral	39 (48.8)
Dissatisfied	3 (3.8)
CAM related adverse event	
Yes	3 (3.8)
None	77 (96.2)
Disclosure of CAM use to primary doctor	
Yes	23 (28.8)
No	57 (71.2)
Reason for not disclose to doctor	
Unnecessary	10 (12.5)
Not been asked	66 (82.5)
Unknown	4 (5.0)

cyclophosphamide. Two third of patients had localized or loco-regional disease. There were 80 (44.2%) and 101 (55.8%) Cam users and non-CAM users, respectively. More patients lived in capital city, Bangkok, in CAM users compared to non-CAM users (57.5% vs. 34.7%, p=0.019). Although not statistically significant, there were more patients with breast cancer in non-CAM users. Baseline characteristics in CAM users and non-CAM users were shown in Table 1.

To improve efficacy, decrease toxicity, and decrease worry and fear of conventional therapy were the most common reason for CAM use in this study. Herbal medicine is the most common type of CAM used among our patients. Almost all patients did not complaint any adverse event related to CAM use. Most patients (71.3%) did not inform their doctors regarding the CAM use. The CAM use detail was shown in Table 2.

Among CAM users, there were 76 (95%) and 72 (90%) patients receiving second and third cycles, respectively. There were 97 (96%) and 92 (91%) non-CAM users receiving second and third cycles, respectively. The reasons for not receiving the subsequent cycles were death and/or disease progression in five and two patients in CAM users and non-CAM users, respectively. Three CAM users and seven non-CAM users did not show up on the subsequent chemotherapy dates. Among 173 patients receiving at least two cycles of chemotherapy, the chemotherapy was delayed and/or reduced in 40 (52.6%) CAM users and 48 (49.5%) non-CAM users, p =0.681. However, there were the trends toward more CAM users having schedule delay for more than 2 times, schedule delay longer than 14 days and more than 20% dose reduction. The chemotherapy schedule delay and

Table 3. Association between CAM Use and Chemotherapy Schedule Delay and Dose Reduction

	CAM users n=76 (%)	Non-CAM users n=97 (%)	p-value
Schedule delay and/or dose reduction	40 (52.6, 95% CI 41.2-64.1)	48 (49.5, 95% CI 39.4-59.6)	0.681
Dose reduction			
Any dose reduction	30 (39.5, 95% CI 28.2-50.7)	36 (37.1, 95% CI 27.3-49.6)	0.751
More than 20%	6 (7.9, 95% CI 1.7-14.1)	2 (2.0, 95% CI -0.8-4.9)	0.068
Schedule delay			
Any delay	22 (28.9, 95% CI 18.5-39.4)	27 (27.8, 95% CI 18.8-36.9)	0.872
More than 2 times	4 (5.3, 95% CI 0.1-10.4)	1 (1.0, 95%CI -1.0-3.1)	0.094
Longer than 14 days	9 (11.8, 95% CI 4.4-19.3)	4 (4.1, 95%CI 0.1-8.2)	0.056

Table 4. Association between CAM Use and Chemotherapy Dose Intensity

Mean Relative dose intensity (RDI)	CAM users	Non-CAM users	p-value
Overall	(n=69)	(n=91)	
Dose Intensity	92.4% (95%CI 90.2-94.4)	94.1% (95%CI 92.3-95.9)	0.244
Less than 90% RDI	24 (34.8%, 95% CI 23.3-46.3)	18 (19.8%, 95%CI 11.4-28.1)	0.033
Adriamycin and cyclophosphamide	(n=36)	(n=58)	
Dose Intensity	91.9% (95% CI 89.5-94.2)	94.4% (95%CI 92.1-96.8)	0.171
Less than 90% RDI	15 (41.7%, 95% CI 24.8-58.6)	11 (19.0%, 95% CI 8.6-29.4)	0.017
Other regimens	(n=33)	(n=33)	
Dose Intensity	92.9% (95%CI 89.1-96.4)	93.4% (95% CI 90.3-96.1)	0.962
Less than 90% RDI	9 (27.3%, 95% CI -11.2-43.3)	7 (21.2%, 95%CI 6.5-35.9)	

Table 5. All Grades of Adverse Event

Adverse event	CAM users (N=79)	Non-CAM users (N=98)	p-value
Anemia			
All grade	50 (63.3%)	52 (53.1%)	0.171
Grade 3 – 4	4 (5.1%)	0	0.024
Neutropenia			
All grade	48 (60.8%)	60 (61.2%)	0.949
Grade 3 – 4	30 (38.0%)	28 (28.6%)	0.185
Thrombocytopenia			
All grade	17 (21.5%)	18 (18.4%)	0.601
Grade 3 – 4	2 (2.5%)	2 (2.0%)	0.827
Increased aspartate aminotransferase			
	(N=71)	(N=87)	
All grade	16 (22.5%)	11 (12.6%)	0.100
Grade 3 – 4	1 (1.4%)	0	0.267
Increased alanine aminotransferase			
	(N=71)	(N=87)	
All grade	17 (23.9%)	11 (12.6%)	0.064
Grade 3 – 4	3 (4.2%)	0	0.053
Increased alkaline phosphatase			
	(N=71)	(N=87)	
All grade	11 (15.5%)	8 (9.2%)	0.517
Grade 3 – 4	1 (1.4%)	0	0.267
Blood bilirubin increased			
	(N=71)	(N=87)	
All grade	5 (7.0%)	9 (10.3%)	0.467
Grade 3 – 4	2 (2.8%)	1 (1.1%)	0.445
Fever			
Grade 1	12 (15.2%)	10 (10.2%)	0.318
None	67 (84.8%)	88 (89.8%)	
Febrile neutropenia			
Yes	3 (3.8%)	4 (4.1%)	0.923
No	76 (96.2%)	94 (95.9%)	
Mucositis			
All grade	24 (30.4%)	26 (26.5%)	0.488
Grade 3 – 5	1 (1.3%)	0	0.264
Nausea			
All grade	41 (51.9%)	56 (57.1%)	0.485
Grade 3	3 (3.8%)	1 (1.0%)	0.217
Vomiting			
All grade	25 (31.6%)	34 (34.7%)	0.758
Grade 3 – 5	3 (3.8%)	1 (1.0%)	
Diarrhea			
All grade	12 (15.2%)	13 (13.3%)	0.217
Grade 3 – 5	0	1 (1.0%)	0.843
Anorexia			
All grade	57 (72.2%)	67 (68.4%)	0.368
Grade 3 – 5	1 (1.3%)	0	0.584
Malaise			
All grade	52 (65.8%)	60 (61.2%)	0.264
Grade 2	15 (19.0%)	5 (5.1%)	0.398
Myalgia			
All grade	28 (35.4%)	31 (31.6%)	0.097
Grade 2 – 3	7 (8.9%)	3 (3.1%)	

Table 5. Continued

Adverse event	CAM users (N=79)	Non-CAM users (N=98)	p-value
Weight loss			
Yes	43 (54.4%)	55 (56.1%)	0.822
No	36 (45.6%)	43 (43.9%)	

dose reduction data was shown in Table 3.

Among 69 (86%) and 91 (90%) CAM users and non-CAM users receiving four cycles of chemotherapy, the mean RDI was 92.3% and 94.1% in CAM and non-CAM users, respectively, $p=0.244$. However, as compared with non-CAM users, there were significantly more CAM users receiving chemotherapy less than 90% RDI (34.8% vs 19.8%, $p=0.033$). The chemotherapy RDI was shown in Table 4.

For quality of life assessment, there were 43 and 48 patients in CAM and non-CAM users interviewed at first and third cycles. As compared to first cycle, at third cycle, the mean QOL score was -4.63 (95% CI -2.49-9.27) and -8.02 (-2.36- 9.142) in CAM user and non-CAM user, respectively ($p=0.255$). There were 28 (65.1%) CAM users and 36 (75.0%) non-CAM users having decreased quality of life score at third cycle ($p=0.303$).

Overall adverse event rates in both groups were similar. As compared to non-CAM users, more CAM users developed grade 3 or 4 anemia (5.1% vs 0, $p=0.024$). There was a trend toward more increased aminotransferase in CAM users compared to non-CAM users. CAM users had significantly more grade 2 malaise than non-CAM users, (19.0% vs 5.1%, $p=0.004$). The adverse event data was shown in Table 5.

Discussion

In this prospective study, we compared chemotherapy treatment delivery between CAM users and non-CAM users. There was no difference in overall rates of chemotherapy schedule delay or dose reduction between these two groups. However, there were significantly more patients receiving chemotherapy with less than 90% relative dose intensity in CAM users. As compared to non-CAM users, CAM users had higher rates of some adverse events during chemotherapy.

Among 181 cancer patients receiving chemotherapy, 44.2% of patients were using CAM. It was less than 60.9% of Thai cancer patients receiving radiotherapy in previous report.(Puataweepong et al., 2012) Besides the population difference, the face-to-face interviewing in the chemotherapy center in this study might result in the less number of patients reporting CAM use than using self-report method in previous study.

The overall rates of chemotherapy schedule delay and dose reduction, and mean relative dose intensity were not different between CAM and non-CAM users. However, there were significantly more patients receiving chemotherapy less than 90% RDI in CAM users. This was likely related to a trend toward more major chemotherapy modification including more-than-2-times or longer-than-14-day schedule delay or more than

20%-dose reduction in CAM users. Although, there were more CAM users receiving AC, the difference was still demonstrated in the patients receiving AC. Although all treating oncologists were blinded, there was no standard protocol for chemotherapy modification in this study. Therefore, interpretation of these post-hoc analyses should be cautious with this potential confounding factor. To our knowledge, this is the first study comparing the chemotherapy treatment deliveries between CAM and non-CAM users.

As compared to non-CAM users, there were more incidences in certain adverse events including transaminitis, anemia and malaise in CAM users. In CAM users, the incidences of increased aminotransferases were 24-30% compared to 12% in non-CAM users, this might be related to hepatotoxicity of herbal medicine as shown in several reports (Teo et al., 2016; Philips et al., 2019). However, severe transaminitis was quite rare in CAM users in this study. For myelosuppression, there were significantly more severe anemia in CAM users but no difference in neutropenia or thrombocytopenia. Differently, CAM protective effects on chemotherapy induced neutropenia was demonstrated in previous randomized trials and a systemic review (Zhuang et al., 2009; Zhuang et al., 2012; Jia et al., 2015). However, in this study, there was an imbalance in chemotherapy regimens and CAM types were unrestricted. Therefore, these findings should be cautiously interpreted.

In this study, around two third of CAM users did not disclose to their doctors. The CAM use disclosure rates were varied among previous reports.(Shih et al., 2009; Puataweepong et al., 2012; Wode et al., 2019) The major reason for that was no asking by their doctors. Given, the potential adverse effects of CAM in patients receiving chemotherapy, acquiring for CAM using information should be encouraged among oncologists.

Our study had some limitations including no chemotherapy schedule and dose modification protocol, various chemotherapy regimens and possible imbalance of patient characteristics including performance status and comorbidity. Also CAM users might not disclose their CAM use especially with the face-to-face interview method in the chemotherapy center. There was certainly a wide variation in CAM types used by the patients in this study. The study was a single center study, the generalizability might be limited.

In conclusion, this prospective study in Thai patients with cancer demonstrated similar overall rates of chemotherapy schedule delay and dose reduction between CAM users and non-CAM users receiving chemotherapy. However, there were significantly more CAM users receiving chemotherapy less than 90% relative dose intensity. Acquiring of CAM using data should be

encouraged among the oncologists.

Author Contribution Statement

CR and ST contributed to the study conception and design. ST and PW provided the administrative support. All authors contributed to enrollment, provision of study patients and collection and assembly of data. CR and ST contributed to analysis and interpretation of data. All authors wrote the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgements

Funding

This study was funded by “The 90th Anniversary Scholarship”, Ratchadapisek Sompoch Fund Endowment Fund, Chulalongkorn University and Chulalongkorn Medical Oncology Research Fund.

Scientific approval

This study was a part of the approved thesis of Dr. Chawanya Rabilossaporn.

Ethical approval

The study procedures were in accordance with and approved by the Institution Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, and with the 1964 Helsinki declaration.

Consent to participate

Informed consent was obtained from all individual participants included in this study. All authors agreed to published this manuscript.

Data availability and material

Available from the authors on request.

Conflict of Interest

All authors declare that they have no conflict of interest.

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