Indonesian Journal of Clinical Pharmacy, December 2021
Vol. 10 Iss. 4, pg 261–271
ISSN: 2252–6218, e-ISSN: 2337-5701
Available online at:
http://ijcp.or.id
DOI: 10.15416/ijcp.2021.10.4.261
Research Article

Evaluation of Quality of Life on Functional, Symptoms, and Global Health Status in Breast Cancer Patients among Chemotherapy Cycles with Cyclophosphamide-Doxorubicin-5Fluorouracil

Siti Saleha[1], Azizah Vonna[1], Sarah Firdausa[2]
[1]Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Banda Aceh, Indonesia
[2]Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

Abstract
Treatment of breast cancer with chemotherapy in several cycles has led to differences in patients' quality of life. One of the chemotherapy recommendations for breast cancer is Cyclophosphamide-Doxorubicin-5Fluorouracil (CAF). Therefore, this research aimed to determine the quality of life among chemotherapy cycles with CAF in breast cancer patients at Dr. Zainoel Abidin Hospital Banda Aceh. This is an observational analytic study with the cross-sectional method, where 32 patients were obtained through a total sampling technique from June to August 2019. Quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30), while the Kruskal-Wallis test performed the statistical analysis. The results showed that the quality of life of breast cancer patients has no significant difference among chemotherapy cycles with CAF ($p>0,05$). However, some changes in the functional and symptom scale among patients required a further follow-up by healthcare professionals to improve the quality of life.

Keywords: CAF, cycle, QLQ C-30, quality of life

Evaluasi Kualitas Hidup pada Status Fungsional, Gejala, dan Kesehatan Umum pada Pasien Kanker Payudara Antarsiklus Kemoterapi dengan Cyclophosphamide-Doxorubicin-5Fluorouracil

Abstrak
Penggunaan kemoterapi dalam beberapa siklus sebagai pengobatan kanker payudara dapat menimbulkan perbedaan kualitas hidup pasien. Salah satu kemoterapi yang direkomendasikan untuk kanker payudara adalah *Cyclophosphamide-Doxorubicin-5Fluorouracil* (CAF). Tujuan penelitian ini adalah mengetahui perbedaan kualitas hidup pasien kanker payudara antarsiklus dengan kemoterapi CAF di Rumah Sakit Umum Daerah dr. Zainoel Abidin Banda Aceh. Jenis penelitian ini adalah observasional analitik dengan metode *cross-sectional*. Sampel berjumlah 32 pasien yang diperoleh menggunakan teknik total sampling dari bulan Juni sampai Agustus 2019. Penilaian kualitas hidup dilakukan menggunakan *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* (EORTC QLQ C-30) dan analisis statistik menggunakan uji *Kruskall-Wallis*. Hasil penelitian menunjukkan bahwa tidak terdapat perbedaan kualitas hidup yang signifikan antarsiklus pada pasien kanker payudara dengan kemoterapi CAF ($p>0,05$). Meskipun demikian, beberapa perubahan skala fungsional dan gejala yang dirasakan pasien pada tiap siklus kemoterapi yang dihadapi perlu menjadi perhatian bagi tenaga kesehatan dalam rangka meningkatkan kualitas hidup pasien.

Kata kunci: CAF, kualitas hidup, siklus , QLQ C-30

Correspondence: Siti Saleha, S.Farm., Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Banda Aceh, Aceh 23111, Indonesia, email: *salehabuchari@gmail.com*
Submitted: 17th December 2020, Accepted: 12th December 2021, Published: 30th December 2021

Introductions

Breast cancer is an abnormal and uncontrolled cells growth in the breast tissue. Breast cancer is one of the most common cancer types with the highest incidence rate. Data from the Global Cancer Observatory in 2018 showed that the incidence rate of breast cancer is at the second position with a prevalence of 11.6% in the world, and at the first place in Indonesia, with a prevalence of 16.7% (58,256 of 348,809 cases).[1,2] Patients diagnosed with breast cancer have to undergo treatment to recover from cancer cells or avoid the spread throughout the body. One of the treatment modalities in breast cancer patients is chemotherapy (CT). CT is a cancer treatment that uses medications to block or slow down the growth of cancer cells.[3] Chemotherapy in breast cancer patients can be a single agent or combination, but in most cases, chemotherapy is more effective when combined.[4]

Guidelines for Management of Breast Cancer by World Health Organization (WHO) states that one recommended combination of chemotherapy for breast cancer patients is Cyclophosphamide-Doxurubicin-5Fluorouracil (CAF).[5] CAF is also recommended by The Association of Indonesian Oncology Surgeons and The Indonesian Ministry of Health as one of the chemotherapy regimens in breast cancer patients.[6,7] The Indonesian Ministry of Health in its guidelines for breast cancer management states that CAF chemotherapy is one of the first-line therapies for breast cancer patients.[7]

The development of the disease and the use of chemotherapy as a treatment in breast cancer patients are often associated with changes in the quality of life (QoL). QoL is defined as a perception of well-being individuals and satisfaction with their goals, expectations, and standard of living.[8] QoL data may inform healthcare professionals about problems and changes experienced by the patients during treatment. This knowledge may also improve communication between healthcare professionals and patients.[9]

Patients who receive chemotherapy have a course of treatment that includes a number of cycles (CT-cycles), which usually a cycle may last for 3–4 weeks.[10] This situation may cause patients to experience some adverse effects and symptoms that will negatively affect their QoL.[11] Several studies reported that there was a strong correlation between the length of chemotherapy and the QoL of patients.[12,13] However, local data on this matter is still lacking. Therefore, aim of this study was to assess the breast cancer QoL of patients while undergoing CAF chemotherapy at dr. Zainoel Abidin Hospital Banda Aceh.

Methods

In this cross-sectional study, cancer patients undergoing CT-cyles at the chemotherapy unit of dr. Zainoel Abidin Hospital, Banda Aceh from June to August 2019 were recruited according to the following inclusion criteria: women who were diagnosed with breast cancer and received CAF combination chemotherapy, aged greater than 18 years, could communicate and were willing to become respondents by signing informed consent; and exclusion criteria: patients who had metastatic, required walking aids before receiving first cycle of chemotherapy, and had a history of other chronic diseases (such as heart disease, stroke, chronic kidney disease, diabetes, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, epilepsy, chronic obstructive pulmonary disease, asthma, hepatitis B and C, rheumatoid arthritis, and HIV) which were determined based on patients' medical records. A total of 32 patients met the inclusion and exclusion criteria and was included in this study.

The quality of life questionnaire (QLQ) C-30 from The European Organization for Research and Treatment of Cancer (EORTC) was used to asses the QoL of patients, and is

composed of 30 questions divided into three domains, which is functional scales, global health status and symptom scales. Functional scales is composed by 15 questions, global health status is composed by 2 questions and symptom scales is composed by 13 questions. Response of each question was assessed on a Likert scale starting from 1 to 4. The answer is then transformed into scores ranging from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/ problems. This QLQ C-30 is valid and reliable to be used as an instrument in measuring the QoL of cancer patients in Indonesia and has been translated into Indonesian.[14]

The QLQ C-30 was administered by the researcher using the guided interview, where questions were asked directly to the patient. Each patient completed the questionnaire once before they are undergoing their next CT-cycle. The time range between the CT-cycles is 21 days. Statistical analysis was performed using R 3.6.1 program. Shapiro-Wilk normality test was conducted to obtain the normality of QoL data in each cycle. The calculation of the QoL score from the QLQ C-30 was carried out in accordance with the guidelines developed by the EORTC study group and the differences in QoL of patients among cycles were analyzed using Kruskal-Wallis test. $p<0.05$ was considered statistically significant. This study has been approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Syiah Kuala no. 102/PA/FK-RSUDZA/2019.

Results

The patients' characteristics are presented in Table 1, while the differences in QoL of patients among cycles are presented in Table 2. The majority of patients were 40–49 years old (44%), were married (97%), worked as housewife (62%), received chemotherapy adjuvant (69%), diagnosed with right side of breast cancer (62%), invasive ductal carcinoma pathology (85%), and were in the stage IIIb (50%), in which cancer cells have spread to lymph nodes and belong to the locally advanced stage. Patients were grouped according to CT-cycles they have completed. A total of 31%, 16%, 28%, 12.5%, and 12.5% have completed the first, second, third, fourth, and fifth cycle, respectively.

QoL of patients was assessed by the QLQ C-30 questionnaire. Patients responses in questionnaire were divided into 3 scales, that is functional, symptoms and global health status (Figure 1). Differences in breast cancer QoL of patients among cycles were analyzed to determine whether there were differences in QoL after patients undergo the first, second, third, fourth, and fifth CT-cyle. Patients in each cycle experienced changes on all three scales. On a functional scale, the physical, role, and social functions of patients tended to show a better function as the cycle increases, in which patients in the fifth CT-cycle have the best level of function. Nevertheless, there was a decrease in all three functions in the second CT-cycle patients. This condition could occur because patients in the second CT-cycle experienced a high loss of appetite and worse fatigue condition. Both of these can affect the body and patient's ability to be able to perform daily activities. On the other hand, patients in third, fourth, and fifth CT-cycle experienced an increase of physical, role, and social function. It could happen because the body has begun to adapt and tolerate the effects of chemotherapy. In spite of that, no theory has been found to support this hypothesis.

Moreover, patients also experienced changes in emotional function, in which it tended to be unstable with increasing cycles. Nevertheless,

Table 1 Characteristics of the Study Population (N=32)

Characteristics	Number of Patients (n)	Percentage (%)
Age (Years)		
<40	4	12
40–49	14	44
50–59	9	28
≥60	5	16
Marital status		
Unmarried	1	3
Married	31	97
Occupation		
Housewives	20	62
Civil servants	5	16
Farmers	3	9
Enterpreneurs/Daily wage	4	13
Chemotherapy Settings		
Neoadjuvant	10	31
Adjuvant	22	69
Location Diagnosis		
Dextra	20	62
Sinistra	12	38
Pathology Diagnosis		
Non-Residual Ductal Carcinoma In Situ	1	3
Invasive Ductal Carcinoma (IDC)	27	85
Invasive Lobular Carcinoma (ILC)	2	6
Mucinuous Carcinoma	1	3
Clear Cell Carcinoma	1	3
Stage Diagnosis		
IIa	1	3
IIb	6	19
IIIa	8	25
IIIb	16	50
IIIc	1	3
Chemotherapy Cycles		
I	10	31
II	5	16
III	9	28
IV	4	12,5
V	4	12,5

the change is still in good condition, in which the score is ±80. Changes in the emotional function could be caused by the patient's concern regarding his condition and the treatment. This situation will certainly affect the mood and cause anxiety in patients.[15] Similar to emotional function, the cognitive function of the patient is also in good condition, in which the score is ±80. On the symptoms scale, fatigue is the most symptom felt by patients, in which the score is higher than other symptoms. The symptom of fatigue felt by patients in the first, second, and third CT-cycle are worse than the fourth and fifth, but it is not much different, in which the score is around ±40.

In addition, patients also felt the symptoms of pain, dyspnea, and insomnia, but it tended to be unstable as the cycle increases. On the

Table 2 Differences in Patients' Quality of Life among CT-cycles

Scales	p-value
Functional	
Physical function	0.4752
Role function	0.4518
Emotional function	0.2119
Cognitive function	0.4962
Social function	0.2516
Symptom	
Fatigue	0.9351
Nausea-Vomiting	0.5765
Pain	0.3961
Dyspnea	0.5319
Insomnia	0.1209
Appetite loss	0.9506
Constipation	0.4897
Diarrhea	NA
Financial problems	0.08016
Global Health Status	
Quality of life	0.9188

symptom of pain, patients in the first, third, and fourth CT-cycle felt worse pain than the other cycles. Pain could happen due to cancer itself and the effect of chemotherapy. On the symptom of dyspnea, patients in the third and fifth CT-cycle felt worse dyspnea than the other cycles.

Patients in this study also felt a symptom of insomnia. Generally, insomnia is often associated with emotional conditions such as anxiety. Insomnia felt by the patients in the first, second, and third CT-cycle can be affected by the presence of pain, whereas in the fourth and fifth CT-cycle, insomnia is no longer affected by pain and it is difficult to explain. In spite of that, one of the causes that could be suspected is the symptom of dyspnea that is still felt.

In addition to the symptoms scale mentioned earlier, gastrointestinal-related symptoms were also assessed. These symptoms include appetite loss, nausea-vomiting, constipation and diarrhea. Appetite loss is the most felt symptom by patients, in which the score is higher than other symptoms. The worst appetite loss felt by patient in the second CT-cycle but then tended to decrease with an increasing cycle, in which patients in the fifth CT-cycle felt the least appetite loss.

Patients in this study also felt symptoms of nausea-vomiting and constipation, in which the level of symptoms tended to be unpredictable and fluctuate. On the symptom of nausea-vomiting, patients in the first CT-cyle felt worse than the other cycles, whereas patients in the second and fifth CT-cycle felt fewer symptom. However, patients in the third and fourth CT-cycle do not felt nausea-vomiting at all. Besides, patients also felt symptom of constipation, in which patients in the fifth CT-cycle felt worse than the other cycles. Meanwhile, patients from the first to third CT-cycle felt decreased symptoms, instead of patients in the fourth CT-cycle do not felt constipation at all.

Furthermore, patients also felt the symptom of economic conditions, which is financial difficulties. This could probably happen because the patients must undergo chemotherapy in a number of cycles. These conditions make patients have to return to the hospital every 21 days for the next cycle of chemotherapy. Based

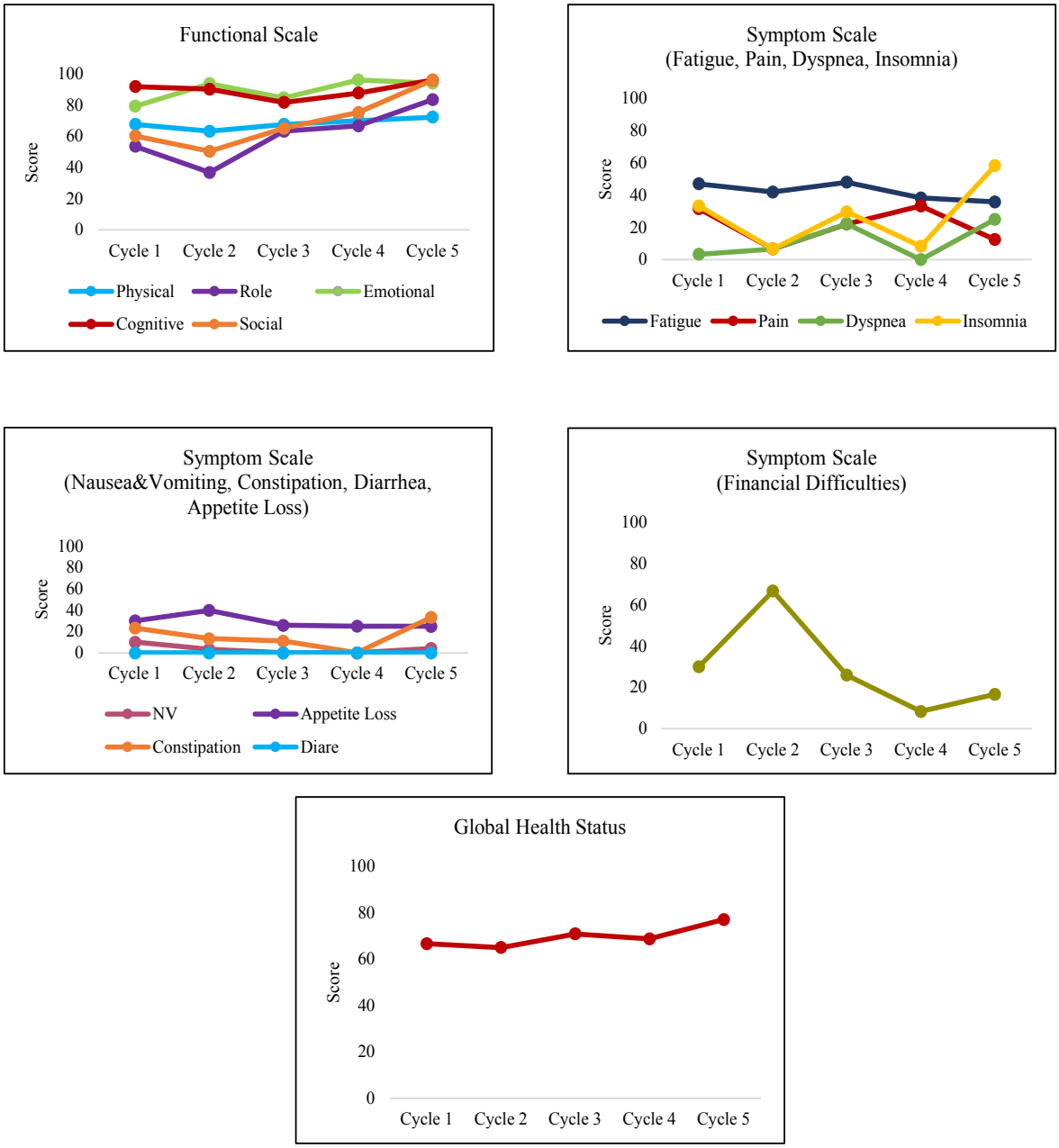

Figure 1 Patients' Quality of Life in Each Scale Among CT-cycles

High score for a functional scale and the global health status represents a high level of functioning and quality of life (QoL), but a high score for a symptom scale represents a high level of symptomatology

on the results, it is known that patients in the fifth CT-cycle have higher global health status than the other cycles. In the fifth CT-cycle, patients have already obtained more than 80% of their chemotherapy regimens. This could probably the reason why patients have a much better health status than before.

Furthermore, data on the QoL of patients in this study were tested for normality and the results showed that the QoL data on the functional, symptoms and global health status were not normally distributed ($p<0.05$, normally distributed if $p>0.05$). Therefore, the analysis of differences in the QoL was

tested using a non-parametric test, which is Kruskal-Wallis. The results showed that although the QoL scores of patients differed in each cycle, these differences were not statistically significant ($p>0.05$) (Table 2). This is indicated by p-value of each scale in functional, symptomatic and global health status which exceeds the significance level of 0.05 ($p>0.05$).

Discussion

Based on the results, there was a change in the patients condition during CT-cycles, indicated by the change in each score. On the cognitive functions, there is an unstable change with increasing cycles. It could be caused by the neurotoxic effects of chemotherapy of patients.[16] Nevertheless, cognitive functions, such as thinking, memory, and language are centered on the cerebral cortex.[17] Therefore, patients in this study still have a good cognitive function, because cancers do not metastasize to the brain and the use of CAF chemotherapy is not directly related to the cerebral cortex.

On symptom scales, the patients also felt some symptoms during CT-cycles, which were fatigue, dyspnea, insomnia, appetite loss, nausea-vomiting and constipation. The first is fatigue, this symptom could be caused by the medical situations, adverse effects of chemotherapy, physical or mental activity, and psychological variables.[18,19] Fatigue in patients undergo CAF chemotherapy occur because cyclophosphamide, doxorubicin, and 5-fluorouracil affect the bone marrow and cause a decrease in blood cells which makes the patient feel weak and tired easily.[20–22] The second is dyspnea, this symptom could happen due to a decrease in hemoglobin in the blood resulting from the process of disease or the use of chemotherapy.[23,24] The third is insomnia, this symptoms have been found to be highly correlated with anxiety and depression.[25,26] However, in this study, it could not be related to their emotional function. This is because the emotional function of the patient is at a good level of function. Therefore, it might be caused by other symptoms felt by patients. The fourth is appetite loss, this symptom could happen because chemotherapy can also affect cells in the digestive tract, causing dry mouth, nausea, vomiting, changed tastes, and slower emptying of the stomach. As a result, the patient becomes unwilling to eat food. This condition could cause patients to experience weight loss and malnutrition.[27–29] Therefore, communication between healthcare professionals and patients is crucial to make sure that they still have a good nutritional intake during chemotherapy. The fifth is nausea-vomiting, these symptoms were not felt by all patients and tended to be unpredictable and fluctuate. This condition could happen due to the risk of side effects of nausea-vomiting with CAF depending on the dose received by the patient.[20–22] The last is constipation, this symptom could happen because constipation caused by a number of reasons, including the type of chemotherapy used, drugs given with chemotherapy to relieve nausea-vomiting, or lack of fluid entering the patients body.[30,31] In addition, patients are also experiencing financial difficulties. The burden of going home and return to the hospital coupled with the work of patients who are predominantly housewives are some contributing factors.

Nevertheless, patients who will undergo the last CT-cyle have higher global health status than the other cycles. This means that patients can enjoy life whole better and more comfortable.[32] On the other hand, the CT-cyle that will soon end may lead to high optimism in patients regarding their health status. This optimism also plays a role in patients in the 5 CT-cycle to felt better global health status even though some symptoms are still felt.

The findings of this study showed that there was no significant difference on the QoL of patients among cycles. Result of a study by

Cherchiglia et al. on differences in patients QoL at 2 time points, which is on the first day of the first and second CT-cyles, showed that there was no significant difference in the general health status of the patient. However, there was a significant difference in emotional function ($p<0.001$), the pain symptom ($p=0.001$), the symptoms nausea and vomiting ($p<0.001$) and diarrhea ($p=0.014$).[33] In contrast, Juwita et al. showed that the QoL of patients in each cycle of chemotherapy had a significant difference at each scale ($p<0.05$).[34] Heydarnajed et al. showed that there was a significant difference ($p<0.001$) among the QoL of patients undergo the ≤2 and 3-5 cycles.[35] Hassen et al. showed that the QoL of patients receiving ≤ 2 CT-cyle had significantly lower scores.[36] The difference in this study with previous studies may be due to the type of cancer and the specific chemotherapy received by patients. Patients in this study were breast cancer patients with CAF combination chemotherapy, while the criteria of patients in others study were non-specific, there were patients with any type of cancer and undergoing any chemotherapy both single and combination.

One confounding factor that potentially contributed to difference between the results of this study and other studies is disease severity (include stage and pathology of diagnosis). Disease severity among patients distributed unequally between study groups and was also related to both chemotherapy cycle and QoL patients.[37] The majority of patients were in stage IIIb with invasive ductal carcinoma pathology, this could affect QoL of patients during the chemotherapy cycle, thus leading to a QoL score that did not statistically significant.

The difference in the QoL scores of cancer patients while undergoing chemotherapy remains important and should be a concern, although it does not appear to be statistically significant. Generally, the minimum important difference (MID) ≥5 points from the QLQ C-30 score, is considered to be able to explain clinically meaningful differences. Cocks et al. also provide guidelines for determining clinically significant differences from each QLQ C-30 scale.[38]

Our study had limitations. This study assesses the overall QoL of breast cancer patients, so those specific issues were not evaluated in further detail. Generalizing the results nationwide should be done cautiously since these findings were obtained from one hospital only.

Conclusions

There is no significant difference in the QoL among cycles ($p>0.05$) in patients receiving cyclophosphamide-doxorubicin-5fluorouracil (CAF) chemotherapy in terms of function scale, symptom scale and global health status assessed. Nevertheless, this study suggests that some changes in the functional and symptom scale between chemotherapy cycles experienced by patients required a further follow-up by healthcare professionals in order to improve QoL of patients.

Acknowledgements

We thank all pharmacy lecturers who provided input and suggestions in this study. We also thank the EORTC who has been willing to answer the author's questions and provide detailed explanations related to the questionnaire in this study.

Funding

The study was not funded by any source of grants.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the study, authorship,

and/or publication of this article.

References

1. WHO International Agency for Research on Cancer. Indonesia [Accessed on: June 2019]. Available at: http://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf
2. WHO International Agency for Research on Cancer. New global cancer data [Accessed on: June 2019]. Available at: https://www.uicc.org/new-global-cancer-data-globocan-2018
3. Sugerman DT. Chemotherapy. J Am Med Assoc 2013;310(2):218. doi: 10.1001/jama.2013.5525
4. Fisusi AF, Emmanuel OK. Drug combinations in breast cancer therapy. Pharm Nanotechnol. 2019;7(1):3–23. doi: 10. 2174/2211738507666190122111224
5. World Health Organization. Guidelines for management of breast cancer [Accessed on: April 1, 2019]. Available at: http://applications.emro.who.int/dsaf/dsa697.pdf
6. Manuaba TW. Panduan penatalaksanaan kanker solid PERABOI. Jakarta: Sagung Seto; 2010.
7. Kementerian Kesehatan Republik Indonesia. Panduan penatalaksanaan kanker payudara [Accessed on: March 1, 2019]. Available at: http://kanker.kemkes.go.id/guidelines/PPKPayudara.pdf
8. Abdollahzadeh F, Aghahossini SS, Rahmani A, Kermani IA. Quality of life in cancer patients and its related factors. J Caring Sci. 2012;1(2):109–14.
9. King S, Exley J, Parks S, Ball S, Bienkowska-Gibbs T, MacLure C. The use and impact of quality of life assessment tools in clinical care settings for cancer patients, with a particular emphasis on brain cancer: Insights from a systematic review and stakeholder consultations. Qual Life Res. 2016;25(9):2245–56. doi: 10.1007/s11136-016-1278-6
10. Zhu J, Liu R, Jiang Z, Wang P, Yau Y, Shen Z. Optimization of drug regimen in chemotherapy based on semi-mechanistic model for myelosuppression. J Biomed Inform. 2015;57:20–7. doi: 10.1016/j.jbi.2015.06.021
11. Paraskevi T. Quality of life outcomes in patients with breast cancer. Oncol Rev. 2012;6(1):e2. doi: 10.4081/oncol.2012.e2
12. Damodar G, Smitha T, Gopinatha S, Vijayakumar S, Yedukondala AR. Assessment of quality of life in breast cancer patients at a tertiary care hospital. Arch Pharm Pract. 2013;4(1):15–20.
13. Agustini DD, Surahman E, Abdulah R. Kualitas hidup pasien kanker payudara dengan terapi kombinasi fluorouracil, doxorubicin, dan cyclofosfamide. Indones J Clin Pharm. 2015;4(3):175–85. doi: 10.15416/ijcp.2015.4.3.175
14. Perwitasari DA, Atthobari J, Dwiprahasto I, Hakimi M, Galderblom H, Putter H, et al. Translation and validation of EORTC QLQ-C30 into Indonesian version for cancer patients in Indonesia. Jpn J Clin Oncol. 2011;41(4):519–29. doi: 10.1093/jjco/hyq243
15. Conley CC, Bishop BT, Andersen BL. Emotions and emotion regulation in breast cancer survivorship. Healthcare (Basel). 2016;4(3):56. doi: 10.3390/healthcare4030056
16. Muniyandi DK, Ganesan RM, Meenakshisundaram M, Palanichamu S. Effect of cancer chemotherapy on cognitive function. Int J Cancer Res. 2018;14(2) :52–7. doi: 10.3923/ijcr.2018.52.57
17. Javeed K, Reddy V, Forshing L. Neuroanatomy, cerebral cortex [Accessed on: August 2019]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537247/
18. Manir KS, Bhadra K, Kumar G, Manna A, Patra NB, Sarkar SK. Fatigue in breast

cancer patients on adjuvant treatment: Course and prevalence. Indian J Palliat Care. 2012;18(2):109–16. doi: 10.4103/0973-1075.100826
19. Tabrizi FM, Alizadeh S. Cancer related fatigue in breast cancer survivors: In correlation to demographic factors. Maedica (Bucur). 2017;12(2):106–11.
20. British Columbia Cancer Agency. Cancer drug manual: Cyclophosphamide [Accessed on: April 2019]. Available at: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Cyclophosphamide_monograph_1June2013_formatted.pdf
21. British Columbia Cancer Agency. Cancer drug manual: Doxorubicin [Accessed on: April 2019]. Available at: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Doxorubicin_monograph.pdf
22. British Columbia Cancer Agency. Cancer drug manual: Fluorouracil [Accessed on: April 2019]. Available at: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Fluorouracil_monograph.pdf
23. Pourali L, Taghizadeh A, Akhoundi MR, Varshoei F, Zarifian A, Andalibi MSS. Frequency of chemotherapy induced anemia in breast cancer patients. Int J Cancer Manag. 2017;10(1):e4672. doi: 10.17795/ijcp-4672.
24. Rodgers GM, Becker PS, Blinder M, Cella D, Chanan-Khan, A, Cleeland C, et al. Cancer- and chemotherapy-induced anemia. J Natl Compr Canc Netw. 2012; 10(5):628–53.
25. Trill MD. Anxiety and sleep disorders in cancer patients. Eur J Cancer Suppl. 2013;11(2):216–24. doi: 10.1016/j.ejcsup.2013.07.009
26. Oh CM, Kim HY, Na HK, Cho KH, Chu MK. The effect of anxiety and depression on sleep quality of individuals with high risk for insomnia: A population-based study. Front Neurol. 2019;10:849. doi: 10.3389/fneur.2019.00849
27. Marinho EdC, Custodo IDD, Ferreira IB, Crispim CA, Paiva CE, Maia YCdP. Impact of chemotherapy on perceptions related to food intake in women with breast cancer: A prospective study. PLoS One. 2017;12(11):e0187573. doi: 10.1371/journal.pone.0187573.
28. Muscaritoli M, Lucia S, Farcomeni A, Lorusso V, Saracino V, Barone C, et al. Prevalence of malnutrition in patients at first medical oncology visit: The PreMiO study. Oncotarget. 2017;8(45):79884-96. doi: 10.18632/oncotarget.20168
29. Cooper C, Burden ST, Cheng H, Molassiotis A. Understanding and managing cancer-related weight loss and anorexia: insights from a systematic review of qualitative research. J Cachexia Sarcopenia Muscle. 2015;6(1):99–111. doi: 10.1002/jcsm.12010
30. McQuade RM, Stojanovska V, Abalo R, Bornstein JC, Nurgali K. Chemotherapy-induced constipation and diarrhea: Pathophysiology, current and emerging treatments. Front Pharmacol. 2016;7:414. doi: 10.3389/fphar.2016.00414
31. Wickham RJ. Managing constipation in adults with cancer. J Adv Pract Oncol. 2017;8(2):149–61.
32. Chaturvedi SK, Muliyala KP. The meaning in quality of life. J Psychosoc Rehabilitation Ment Health. 2016;3(2): 47–9. 10.1007/s40737-016-0069-2
33. Cherchiglia ML. Moreira DP, Simino GP. Quality of life of patients with cancer undergoing chemotherapy in Belo Horizonte Hospitals. Value Health 2018; 21(1):S39. doi: 10.1016/j.jval.2018.04.321
34. Juwita AD, Almahdy, Afdhila R. Pengaruh karakteristik pasien terhadap kualitas hidup terkait kesehatan pada pasien kanker payudara di RSUP Dr.M.

Djamil Padang, Indonesia. J Sains Farmasi Klinis. 2018;5(2):126–33. doi: 10.25077/jsfk.5.2.126-133.2018
35. Heydarnajed MS, Hassanpour, Solati DK. Factors affecting quality of life in cancer patients undergoing chemotherapy. Afr Health Sci. 2011;11(2):266–70.
36. Hassen AM, Taye G, Gizaw M, Hussien FM. Quality of life and associated factors among patients with breast cancer under chemotherapy at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia. PLoS One. 2019;14(9):e0222629. doi: 10.1371/journal.pone.0222629
37. Nørgaard M, Ehrenstein V, Vandenbroucke JP. Confounding in observational studies based on large health care databases: Problems and potential solutions-a primer for the clinician. Clin Epidemiol. 2017; 9:185–93. doi: 10.2147/CLEP.S129879
38. Cocks K, Madeleine KM, Galina V, Marissa MM, Peter M, Julia MB. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol. 2011; 29(1):89–96. doi: 10.1200/JCO.2010.28.0107