EJMI

DOI: 10.14744/ejmi.2023.59404
EJMI 2024;8(1):1–7

Research Article

Does Haematological Toxicity Increase with the Use of Lipophilic Chemotherapeutic Agents in Obese Breast Cancer Patients?

Duygu Bayir Garbioglu

Department of Medical Oncology, Zonguldak Bulent Ecevit University Faculty of Medicine, Zonguldak, Türkiye

Abstract

Objectives: In our study, we aimed to investigate the relation between obesity and haematological toxicities evaluated after chemotherapy treatment with lipophilic chemotherapy given according to actual body surface area in breast cancer (Bca) patients with different stages and subtypes and its reflection on overall survival.

Methods: 419 patients who received lipophilic chemotherapy regimens as the first serial chemotherapy regimen, who were not treated with primary granulocyte colony-stimulating factor (G-CSF) and whose haematological parameters were evaluated after the first course of treatment were included in the study.

Results: It was found that 36.8% of 419 patients included in the study were obese. There was no difference between the groups in baseline clinicopathological characteristics except for age. There was a positive correlation between age and BMI values (r=0.254 p<0.001). Grade 3 and grade 4 neutropenia were observed more frequently in normal/underweight patients (p<0.05). Multivariate cox regression analysis showed that grade 3 thrombocytopenia affected survival 17.398 and grade 4 thrombocytopenia affected survival 14.004 times more negatively than grade 0 thrombocytopenia (p<0.001, p<0.001, respectively).

Conclusion: No increase in toxicity or worsening of survival was observed with lipophilic chemotherapy agents given according to actual BSA in obese BCa patients with different stages and immunohistochemical subtypes.

Keywords: Breast cancer, chemotherapy toxicity, obesity, lipophilic agents

Cite This Article: *Bayir Garbioglu D. Does Haematological Toxicity Increase with the use of Lipophilic Chemotherapeutic Agents in Obese Breast Cancer Patients? EJMI 2024;8(1):1–7.*

Obesity is a serious public health problem in most industrialised countries. According to data from the World Health Organization (WHO), obesity has almost tripled worldwide since 1975 and has become the fifth leading cause of global mortality.[1] Obesity is known to be linked to health problems including heart disease, diabetes and cancer, as well as cancer-specific mortality.[2,3] The fact that BCa is the most common type of cancer and the second most common cause of death in developed countries and obesity is an important risk factor in the development of postmenopausal BCa increases the importance of the subject.[4] In our country, it was determined that obesity increased the risk of postmenopausal BCa by 16.2%.[5] On the other hand, obesity was found to be associated with regional recurrence, distant metastasis and BCa-specific mortality in early stage BCa patients treated

Address for correspondence: Duygu Bayir Garbioglu, MD. Zonguldak Bulent Ecevit Universitesi Tip Fakultesi Tibbi Onkoloji Anabilim Dali, Zonguldak, Türkiye
Phone: +90 372 261 20 02 **E-mail:** duygubayir@hotmail.com

Submitted Date: August 27, 2023 **Accepted Date:** September 17, 2023 **Available Online Date:** October 26, 2023

with curative intent.[6] In addition to well-defined prognostic factors such as tumour diameter, lymph node status, histological type, immunophenotypic characteristics, the discovery of new biological and clinical predictors is one of the main goals of studies to improve the overall management of BCa. In this context, overweight, obesity, weight gain and body composition measurements draw attention as potential prognostic and predictive factors in BCa.[7] In current practice, the BSA recommended for chemotherapy dosing based on animal and human studies conducted decades ago is used.[8] Although the importance of maintaining the chemotherapy dose calculated according to BSA has been emphasised, studies have shown that clinicians reduce the dose in overweight and obese patients.[9] It is thought that dose reduction in systemic chemotherapy is an important factor in the increase in cancer-related mortality in overweight and obese patients.[10] The 2012 guideline of the American Society of Clinical Oncology recommends that when the goal is curative treatment, chemotherapy should be dosed according to BSA calculated according to actual total body weight.[11] In addition, there is limited information on the effect of obesity on the pharmacokinetics of chemotherapeutic agents, and there are different information in the literature that especially lipophilic drugs may increase haematological toxicity in obese patients.

In our study, we aimed to investigate the relation between obesity and haematological toxicities evaluated after the first course of lipophilic chemotherapy treatment given according to actual BSA in BCa patients with different stages and subtypes and its reflection on overall survival.

Methods

Local Ethics Committee approval (Date: 15.02.2022 decision no: 34, number: E-25403353-050.99-305317) was obtained before the study, which was planned as a retrospective cohort study, and the Helsinki Declaration criteria were taken into consideration. A total of 985 patients diagnosed with BCa between 2010 and 2021 at Eskisehir Osmangazi University Faculty of Medicine, 419 patients who received lipophilic chemotherapy regimens (AC, EC, DC and paclitaxel) as the first serial chemotherapy regimen, who were not treated with primary G-CSF and whose haematological parameters were evaluated after the first course of treatment were included in the study. The clinical staging of the patients was performed according to the pathological findings in accordance with the 8th The American Joint Committee on Cancer (AJCC 2017) criteria. Clinicopathological characteristics of the patients including age, disease stage, first serial chemotherapy regimens and cycles, neoadjuvant treatment status, and menopausal status were collected. The pre-treatment BMI of the patients was calculated by dividing the body weight measured at the time of diagnosis by the height squared. All patients were divided into three groups as normal or underweight (<25 kg/m^2), overweight (≥25 kg/m^2 and <30 kg/m^2) and obese (≥30 kg/m^2) according to the BMI criteria recommended by the WHO.[12] In addition, BSA of the patients was calculated according to the Dubois formula which is accepted in the literature. (DuBois formula: BSA (m^2) = 0.007184 x (patient's height in cm) 0.725 x (patient's weight in kg)0.425).[13] BCa subtypes were defined as luminal-like (ER/PR+ and HER2-), HER2/luminal (ER/PR+ and HER2+), HER2-type (ER/PR- and HER2+), and TN (ER/PR- and HER2-). Anemia, leucopenia and thrombocytopenia that developed after the first course of chemotherapy were graded according to the CTCAE v5.0.

Statistical Analysis

Mean standard deviation, median, minimum, maximum values were given in descriptive statistics related to continuous data, and number and percentage values were given in discrete data. Shapiro-Wilk test was used to examine the conformity of continuous data to normal distribution. One-way analysis of variance was used to compare the ages of normal, overweight and obese patients. Tukey's test was used to analyse which groups the difference originated from. Chi-Square/Fisher's Exact test was used for group comparisons of nominal variables (cross tabulations). Kaplan-Meier survival analysis and log rank method were used to analyse the differences in survival between independent groups. In addition, Cox regression analysis method was used to determine the factors affecting survival. IBM Statistical Package for the Social Science Statistics for Windows version 20 (Chicago, IL, USA) was used in the evaluations and $p<0.05$ was accepted as the statistical significance limit.

Results

The study included 419 female patients diagnosed with BCa. The mean follow-up period was 4.20±4.18 years. The mean age of the patients was 51.32±11.52 years and the minimum age was 23 years and the maximum age was 86 years. The mean BMI of the patients was 28.61±5.85 (kg/m^2) and 36.8% of the patient population was obese. The rate of stage 1 patients was 17.9%, stage 2 patients was 46.6%, stage 3 patients was 28.3%, and stage 4 patients was 7.2%, and 50.8% of the patients were in the postmenopausal period. When tumour subtypes were analysed, 44.6% were luminal-like (patient and tumour

Table 1. Patient characteristics

n=419	Mean±SD Median (Min-Max)	
Age at diagnosis (year)	51.32±11.52 51 (23-86)	
Weight (kg)	72.18±13.69 72 (40-137)	
Height (cm)	159.14±6.72 160 (136-177)	
BMI	28.61±5.85 28.40 (15.06-59.30)	
BSA	1.74±0.15 1.75 (1.30-2.32)	
Follow-up period (years)	4.20±4.18 3.0 (0-25.1)	
	n	**%**
BMI		
Normal/underweight (<25 kg/m^2)	121	28.8
Overweight (25-30 kg/m^2)	144	34.4
Obese (≥30 kg/m^2)	154	36.8

SD: standard deviation; BMI: body mass index; BSA: body surface area.

Table 2. Disease stages and tumor characteristics

	n	**%**
Metastasis development		
No	358	85.4
Yes	61	14.6
Diagnostic Stage		
Stage 1A	72	17.2
Stage 1B	3	0.7
Stage 2A	118	28.2
Stage 2B	77	18.4
Stage 3A	68	16.2
Stage 3B	6	1.4
Stage 3C	45	10.7
Stage 4	30	7.2
Sub Type		
Luminal-like	187	44.6
HER2/Luminal	155	37.0
HER2	31	7.4
Triple negative	46	11.0
Menopause in Diagnosis		
Premenopausal	149	35.6
Perimenopausal	57	13.6
Postmenopausal	213	50.8

characteristics are summarised in Table 1 and Table 2). The chemotherapy regimens received by the patients in the first series are summarised in Table 3. It was found

Table 3. Patients' first serial chemotherapy treatments and outcome characteristics

	n	**%**
Neo-adjuvant treatment		
No	387	92.4
Yes	32	7.6
Adriamycin-Cyclophosphamide		
No	202	48.2
Yes	217	51.8
Paclitaxel		
No	223	53.2
Yes	81	46.8
Docetaxel-Cyclophosphamide		
No	399	95.2
Yes	20	4.8
Epirubicin- Cyclophosphamide		
No	318	75.89
Yes	101	24.11
Mortality		
Alive	390	93.1
Exitus	29	6.9

that 6.9% of the patients died during follow-up. There was a difference between neutropenia grades of normal, overweight and obese patients ($p<0.05$). The rate of grade 0 neutropenia was higher in obese patients, while the rate of grade 3 and grade 4 was lower. No difference was found between the thrombocytopenia and anaemia grades of normal/underweight, overweight and obese patients ($p>0.05$) (summarised in Table 4). No difference was found between the metastasis, mortality rates, tumour subtypes and menopausal status of the patients according to their BMI ($p>0.05$). (Results are summarised in Table 5). There was no correlation between BMI and survival ($p>0.05$) and also there was no correlation between neutropenia grade and survival ($p>0.05$). There was a correlation between the degree of thrombocytopenia and survival ($p<0.001$). There was a correlation between anemia grades and survival ($p<0.001$). There was no correlation between subtypes and survival ($p>0.05$). There was no correlation between menopause and survival ($p>0.05$). (Results are summarised in Table 6). There was a positive correlation between age and BMI values ($r=0.254$ $p<0.001$). BMI values increased as the age of the patients increased. Multivariate Cox regression analysis showed that grade 3 thrombocytopenia affected survival 17.398 and grade 4 thrombocytopenia affected survival 14.004 times more negatively than grade 0 thrombocytopenia ($p<0.001$, $p<0.001$, respectively) (Results are summarised in Table 7).

Table 4. Comparison of haematological toxicity after lipophilic chemotherapy agent in patients according to BMI values (normal/underweight, overweight and obese)

	Normal/underweight Mean±SD Median (Min-Max)		Overweight Mean±SD Median (Min-Max)		Obese Mean±SD Median (Min-Max)		p
Age	47.45±11.57 46 (23-77)		51.90±10.90 51 (28-86)		53.83±11.32 53.5 (24-83)		<0.001 *
	n	%	n	%	n	%	
Neutropenia							
Grade 0	40	33.1	58	40.3	80	51.9	0.033 **
Grade 1	16	13.2	16	11.1	19	12.3	
Grade 2	12	9.9	17	11.8	20	13.0	
Grade 3	25	20.7	25	17.4	14	9.1	
Grade 4	28	23.1	28	19.4	21	13.6	
Thrombocytopenia							
Grade 0	97	80.2	117	81.2	134	87.0	0.794 **
Grade 1	12	9.9	13	9.0	8	5.2	
Grade 2	5	4.1	4	2.8	5	3.2	
Grade 3	2	1.7	3	2.1	1	0.6	
Grade 4	5	4.1	7	4.9	6	3.9	
Anemia							
Grade 0	14	11.6	22	15.3	24	15.6	0.922 **
Grade 1	57	47.1	68	47.2	79	51.3	
Grade 2	43	35.5	44	30.6	42	27.5	
Grade 3	5	4.1	6	4.2	6	3.9	
Grade 4	2	1.7	4	2.8	3	1.9	

SD:standad deviation; *: one-way analysis of variance (ANOVA); **: Chi-Square Test/Fisher's Exact Test.

Table 5. Comparison of disease characteristics of patients according to BMI values (normal/underweight, overweight and obese)

	Normal		Overweight		Obese		p
	n	%	n	%	n	%	
Metastasis							
No	104	86.0	118	81.9	136	88.3	0.292 *
Yes	17	14.0	26	18.1	18	11.7	
Mortality							
Alive	110	90.9	135	93.8	145	94.2	0.292 *
Ex	11	9.1	9	6.2	9	5.8	
Sub Type							
Luminal-like	48	39.7	64	44.4	75	48.7	0.877 *
HER2/Luminal	49	40.5	54	37.5	52	33.8	
HER2	9	7.4	11	7.6	11	7.1	
Triple negative	15	12.4	15	10.4	16	10.4	
Menopause in Diagnosis							
Premenopausal	54	44.6	50	34.7	45	29.2	0.092 *
Perimenopausal	15	12.4	22	15.3	20	13.0	
Postmenopausal	52	43.0	72	50.0	89	57.8	

*: Chi-Square Test.

Table 6. Survival comparison of patient characteristics

	n (ex)	Mean survival (months±SE)	95 % CI	Log Rang p
Overall		419/29	21.76±0.76	20.27-23.25
BMI				
Normal	121/11	21.38±1.19	19.04-23.72	0.729
Overweight	144/9	17.41±1.07	15.30-19.52	
Obese	154/9	17.54±0.54	16.47-18.61	
Neutropenia				
Grade 0	178/10	22.84±0.83	21.19-24.48	0.097
Grade 1	51/0	-	-	
Grade 2	49/4	12.74±1.12	10.54-14.93	
Grade 3	64/6	12.19±0.90	10.41-13.96	
Grade 4	77/9	9.83±0.67	8.51-11.15	
Thrombocytopenia				
Grade 0	348/11	22.99±0.85	21.33-24.66	<0.001
Grade 1	33/1	20.49±0.70	19.22-21.86	
Grade 2	14/2	10.22±1.18	7.90-12.54	
Grade 3	6/4	4.05±1.51	1.07-7.02	
Grade 4	18/11	3.73±0.37	2.99-4.46	
Anemia				
Grade 0	60/4	22.69±1.29	20.19-25.23	<0.001
Grade 1	204/5	20.32±0.41	19.52-21.3	
Grade 2	129/8	10.98±0.36	10.26-11.70	
Grade 3	17/6	4.75±0.63	3.50-6.00	
Grade 4	9/6	3.87±0.52	2.83-4.90	
Stage				
Stage 1	75/6	12.62±0.63	11.39-13.86	0.020
Stage 2	195/8	23.61±0.52	22.62-24.69	
Stage 3	119/9	11.90±0.60	10.71-13.90	
Stage 4	30/6	17.74±2.76	12.32-23.16	
Luminal-like	187/14	21.29±1.23	18.87-23.72	0.978
Sub type				
HER2/Luminal	155/10	22.28±0.93	20.44-24.12	
HER2	31/2	7.26±0.45	6.36-8.16	
Triple Negative	46/3	14.04±0.77	12.51-15.56	
Menopause				
Premenopausal	149/5	23.94±0.56	22.84-25.04	0.066
Perimenopausal	57/4	17.31±1.37	14.52-20.01	

BMI: body mass index; CI: confidence interval; SE: standard error.

Discussion

In 419 BCa patients, we did not observe an increase in the frequency of haematological toxicity in the obese patient group after lipophilic chemotherapy regimens given according to the actual BSA calculation. On the contrary, normal/low weight patients showed a trend towards grade 3 and grade 4 neutropenia more frequently than obese patients. The results of studies investigating the effect of obesity on chemotherapy toxicity in BCa patients differ. While toxicity was observed to be increased in obese patients in some of them, some of them resulted in a decrease or no difference in toxicity.[14,15]

In a nested-case-control study conducted by Jean et al. to evaluate the effect of chemotherapy-related toxicities on prognosis in 6248 early-stage BCa patients receiving neo-adjuvant and adjuvant treatment, grade 3 and above neutropenia was shown to be an independent risk factor for relapse-free survival. Normal/low-weight patients showed a tendency for more severe neutropenia compared to obese patients as in our study.[16] This large study

Table 7. Univariate and Multivariate COX regression analysis for survival.

	Univariate			Multivariate		
Factor	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Thrombocytopenia						
Grade 0	1					
Grade 1	1.343	0.172-10.683	0.775	1.347	0.165-10.989	0.780
Grade 2	5.134	1.111-23.720	0.036	4.682	0.922-23.775	0.063
Grade 3	29.873	9.187-97.130	<0.001	17.398	3.726-81.233	<0.001
Grade 4	25.304	9.187-97.130	<0.001	14.004	3.349-58.554	<0.001
Anemia						
Grade 0	1					
Grade 1	1.297	0.291-5.780	0.732	1.344	0.289-6.250	0.705
Grade 2	2.182	0.516-9.225	0.289	1.024	0.200-5.242	0.977
Grade 3	13.812	3.034-62.867	0.001	3.476	0.487-24.797	0.214
Grade 4	20.210	4.454-91.707	<0.001	1.642	0.194-13.924	0.646
Stage						
Stage 2						
Stage 1	2.331	0.807-6.732	0.118	2.544	0.840-7.711	0.099
Stage 3	2.364	0.908-6.160	0.078	1.521	0.530-4.363	0.435
Stage 4	5.046	1.698-14.996	0.004	1.551	0.457-5.263	0.481

HR: hazard ratio; CI: confidence interval.

demonstrates a strong correlation between chemotherapy-induced neutropenia and improved survival. In this context, it provides evidence to support the development of neutropenia-adapted clinical trials to investigate optimal dose calculation and its impact on clinical outcome. This is important in populations such as obesity, which may lead to suboptimal chemotherapy doses. A potential explanation for the correlation of chemotherapy-induced neutropenia with increased survival is that neutropenia may be a marker of cancer stem cell death.[17] Studies have shown that treatment of obese patients with reduced dose chemotherapy leads to cancer recurrence and increased mortality.[18] In the study in which the efficacy of docetaxel, a lipophilic chemotherapeutic, was evaluated with BMI in early stage BCa patients, increased BMI in the docetaxel group was found to be associated with decreased disease-free survival and overall survival.[19] Administration of docetaxel and doxorubicin, which are lipophilic drugs, according to actual BSA was found to be associated with increased drug exposure, especially in obese females. Although it has been suggested that dose calculation for these two agents should be based on lean body area like other agents eliminated from the liver, other studies have suggested that dosing based on actual BSA does not increase toxicity.[20,21] Sparreboom et al. investigated the pharmacokinetics of anticancer agents in obese and non-obese cancer patients and reported that obesity alone did not affect the pharmacokinetics of anticancer agents. In their study, they reported that no difference was observed in toxicity between lipophilic agents including adriamycin, irinotecan, docetaxel, paclitaxel and hydrophilic agents including 5-fluorouracil, carboplatin and cisplatin.[19] In another study, it was reported that lipophilic drugs may have some effect on haematological toxicity.[22]

In our study, it was shown that chemotherapy dosing according to actual BSA did not worsen toxicity and survival in obese BCa patients with different stages and immunohistochemical subtypes.

Conclusion

Although the distribution of some of the drugs used in obese patients changes significantly when the data obtained in existing studies are reviewed, the choice of alternative surface area descriptors for dose calculation in obese patients should be drug-specific. Obesity may possibly affect treatment outcomes through mechanisms that are not clearly related to pharmacokinetic properties in a drug-specific manner. To the best of our current knowledge, it seems important to avoid empirical reduction of drug doses in obese patients in terms of affecting treatment endpoints. Additional prospective studies are needed to develop dosing strategies for each agent in obese patients.

Disclosures

Ethics Committee Approval: Eskisehir Osmangazi University Ethics Committee (Date: 15.02.2022 decision no: 34, number: E-25403353-050.99-305317).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. World Health Organization. Obesity and overweight. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed Aug 1, 2023.
2. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat 2010;123:627-35.
3. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.
4. World Health Organization. Number of new cases and deaths in 2020, both sexes, all ages. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf. Accessed Aug 1, 2023.
5. World Health Organization. Cancer cases among both sexes in 2012 attributable to excess body mass index, shown by anatomical site. Available at: https://gco.iarc.fr/causes/obesity/tools-bars. Accessed Aug 1, 2023.
6. Ewertz M, Jensen MB, Gunnarsdóttir KÁ, Højris I, Jakobsen EH, Nielsen D, et al. Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol 2011;29:25-31.
7. Bradshaw PT, Ibrahim JG, Stevens J, Cleveland R, Abrahamson PE, Satia JA, et al. Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. Epidemiology 2012;23:320-7.
8. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 2003;21:4524-31.
9. Hunter RJ, Navo MA, Thaker PH, Bodurka DC, Wolf JK, Smith JA. Dosing chemotherapy in obese patients: actual versus assigned body surface area (BSA). Cancer Treat Rev 2009;35:69-78.
10. Griggs JJ, Sorbero MES, Lyman GH. Undertreatment of obese women receiving breast cancer chemotherapy. Arch Intern Med 2005;165:1267-73.
11. Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2012;30:1553-61.
12. Weir CB, Jan A. BMI classification percentile and cut off points. (Updated 2023 Jun 26). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2023 Jan. PMID: 31082114.
13. Body surface area for adjustment of drug dose. Drug Ther Bull 2010;48:33-6.
14. Carroll JP, Protani MM, Nguyen L, Cheng ME, Fay M, Saleem M, et al. Toxicity and tolerability of adjuvant breast cancer chemotherapy in obese women. Med Oncol 2014;31:881.
15. Furlanetto J, Eiermann W, Marmé F, Reimer T, Reinisch M, Schmatloch S, et al. Higher rate of severe toxicities in obese patients receiving dose-dense (dd) chemotherapy according to unadjusted body surface area: results of the prospectively randomized GAIN study. Ann Oncol 2016;27:2053-9.
16. Abraham JE, Hiller L, Dorling L, Vallier AL, Dunn J, Bowden S, et al. A nested cohort study of 6,248 early breast cancer patients treated in neoadjuvant and adjuvant chemotherapy trials investigating the prognostic value of chemotherapy-related toxicities. BMC Med 2015;13:306.
17. Rocconi RP, Matthews KS, Kemper MK, Hoskins KE, Barnes MN. Chemotherapy-related myelosuppression as a marker of survival in epithelial ovarian cancer patients. Gynecol Oncol 2008;108:336-41.
18. Lyman GH. Weight-based chemotherapy dosing in obese patients with cancer: back to the future. J Oncol Pract 2012;8:e62-e64.
19. Sparreboom A, Wolff AC, Mathijssen RHJ, Chatelut E, Rowinsky EK, Verweij J, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol 2007;25:4707-13.
20. Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage. Implications for drug therapy. Clin Pharmacokinet 1994;26:292-307.
21. Rosner GL, Hargis JB, Hollis DR, Budman DR, Weiss RB, Henderson IC, et al. Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: results from cancer and leukemia group B study 8541. J Clin Oncol 1996;14:3000-8.
22. Miyahara T, Mochinaga S, Kimura S, Aragane N, Yakabe T, Morita S, et al. Effects of tumor type, degree of obesity, and chemotherapy regimen on chemotherapy dose intensity in obese cancer patients. Cancer Chemother Pharmacol 2013;71:175-82.