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REVIEW

Obesity and chemotherapy administration: between empiric and mathematic method review

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ABSTRACT

Introduction: Obesity is a major risk factor for chronic disease and cancer development. Therapeutic management of obese patients with cancer is a real challenge for physician because of the alteration of antineoplastic pharmacokinetics parameters in this population. In routine clinical practices, chemotherapy doses in obese patients are arbitrarily capped or adjusted to an ideal weight to minimize excessive toxicities.

Material and methods: The main goal of this review is to describe the current state of knowledge concerning the correlation between the adjustment of BSA (capping or ideal weight) and the rates of global toxicities and survival outcomes in obese patients under chemotherapy in different types of cancer. We searched in the Medline database (via PubMed) in order to identify all publications of literature reviews whose subject chemotherapy dosing in obese population.

Results: Only a single study was pointing toward increased of global toxicities of full weight dosing. Furthermore, some studies suggests that the practice of limiting doses in overweight and obese patients may negatively influence the quality of care and outcomes in a constantly increasing population.

Conclusion: This review highlights the lack of prospective studies focusing on chemotherapy methods of administration in obese patients. At this time, there is no prospective study comparing capping and full weight dose chemotherapy administration in obese patient population.

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Introduction

Obesity is both a major public health and a risk factor for chronic disease and cancer development. Strong epidemiological studies have associated obesity to increased cancer incidence and mortality [1]. Meta-analysis of prospective studies indicate that an increase in body mass index (BMI) of 5 kg/m^2 over normal weight is associated to an increase of relative risk for developing cancers [2]. Furthermore, obesity is also recognized as a poor prognosis factor as well as a predicator factor of cancers recurrence [3]. Pathophysiologically, obesity is associated with metabolic dysregulation resulting in increased insulin and IGF-1 (insulin growth factor-1), adipokines, cytokines and pro-angiogenic factors in the bloodstream. All these factors promotes cancer development and progression [4,5] and can promote the development of chemoresistance and a weak response to chemotherapy [4].

In common malignancies treatment, obesity affects pharmacokinetics of antineoplastic agents, by altering tissue distribution and drug elimination [6]. An increase of alpha-1 acid glycoprotein in obese population leads to drug sequestration [7]. A blood flow decrease due to a reduction of tissue irrigation and ventricular performance in obese population may also affect drug distribution and elimination [8]. Thereby, therapeutic management of obesity represents a real challenge for physician.

One of the current methods for evaluating the prescribed chemotherapy dose is the body surface area (BSA), originally developed by Du Bois [9]. This formula dating back to 1916 was validated on nine patients whom weight ranged from 25 to 90 kg and was not designed for obese or underweight population. To date, there are at least 10 formulas estimating the body surface area having different conditions of use [9–16]. For the moment, all these formulas have not been validated by the use of a 3D scanner that would allow an exact measurement of the body surface and the validation of these formulas.

In order to optimize the obesity effects on the pharmacokinetics of drugs, several methods have been developed to calculate the appropriate chemotherapy dose in overweight population. One of these methods is to cap the BSA at 2 m^2 (capping) [17]. Another strategy consists in the use of the ideal weight instead of the actual weight. Practice pattern studies demonstrate that up to 40% of obese patients receive limited doses that are not based on actual body weight [18]. In routine clinical practices, chemotherapy doses in obese patients are arbitrarily capped or adjusted to an ideal weight to avoid excessive toxicities. However, two retrospective studies have shown no increased toxicities in obese patients receiving full weight chemotherapy dose [19,20]. In contrast, the recent GAIN study have shown that

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obese patients receiving dose dense chemotherapy according to their real BSA have a higher risk of developing severe toxicities without influencing survival [21]. Moreover, ASCO guidelines recommend to avoid chemotherapy dose reduction in obese patient, in order to avoid compromising clinical outcomes [18]. Empiric dose reduction may result in underdosing obese patients, which lead to higher rates of recurrence hence a poor prognosis in this population. In context of breast cancer management, a strong significant correlation between dose intensity and disease-free survival (DFS) and overall survival was reported [22]. Currently, there are no official recommendations regarding the use of anybody surface formula in obese patients. Most formulas tend to underestimate body surface area in the obese patients which could result in constant underdosing of chemotherapy prescriptions [18]. It becomes crucial to clarify if obese patient receiving full weight-based chemotherapy are at higher risk for toxicities and recurrence. The goal of this review is to describe the current state of knowledge concerning the correlation between the adjustment of BSA (capping or ideal weight) and the rates of global toxicities and survival outcomes in obese patients under chemotherapy in different types of cancer.

Methods and search strategy

We searched in the Medline database (via PubMed) in order to identify all publications of literature reviews whose subject chemotherapy dosing in obese population. This review of the scientific literature was conducted using the keywords 'Body Mass Index' (MeSH Terms), or 'Body Surface Area' (MeSH Terms), and 'agents, antineoplastic' (MeSH Terms) or 'cancer chemotherapy protocol' (MeSH Terms) and 'Obesity' (MeSH Terms). The period covered stretched from the earliest days of the bank until February 2018. Only satisfactory prospective and retrospective studies respecting our inclusion criteria and focusing on the impact of BSA adjustment on global toxicities rate and survival outcomes in obese population with solids tumors and treated with chemotherapy were selected. Systemic reviews and economic studies have not been retained.

Chemotherapy adjustment doses in different malignancies

This review summarizes selected studies, classified according to the type of cancer

Breast cancer

Breast cancer is the cancer with largest number of studies focusing on the question of the adjustment of BSA in obese or overweight patients. GAIN study enrolled 3023 patients and was initially a prospective randomized phase-III adjuvant trial comparing two types of chemotherapy administration. Data of 555 patients with a BMI $\geq$ 30 were analyzed retrospectively. This study observed an increased rate of global toxicities (especially high grade of hematological toxicities), in obese patients receiving dense chemotherapy according to their real BSA. In a multivariate logistic regression model adjusted for a dose of cyclophosphamide received, BSA adjustment remained an independent predictor factor febrile neutropenia ($p = .012$) and high-grade thrombopenia ($p = .005$) [21]. In another, nonrandomized study, 325 electronic patients records were analyzed. In this study, obese patients ($n = 79$) receiving uncapped chemotherapy did not experience a significant difference in febrile neutropenia rates when compared with overweight ($n = 109$) or normal bodyweight groups ($n = 137$). Furthermore, dose capping was associated with a trend towards lower rates of febrile neutropenia than in other groups and may indicate relative under-dosing of chemotherapy [23].

In contrast, a recent retrospective study of 537 Australian women with nonmetastatic breast cancer and treated with adjuvant chemotherapy showed no significant increased severe toxicities among obese patients with either full or adjusted chemotherapy dose. Interestingly, 50% of reduction febrile neutropenia was observed in obese women; however, no patient with dose-capped develop this adverse event. Full dosing appears to be tolerated as well in obese and normal weight women [24].

Likewise, the analysis of retrospective study of 662 patients included, observed that overweight breast cancer patients receiving adjuvant chemotherapy dose calculated on the basis of their actual weight are not at excessive risk of developing myelossupressive event. This study concluded that patient should receive a complete dose of chemotherapy calculated on the basis of their BSA [25]. In another retrospective study, obese patient who received the required dose of chemotherapy did not significantly shown more grade 3 and 4 toxicities and (12% [12/97] versus14% [22/152] $p = .62$) [26]. Poikonen et al., retrospective study concluded that adjuvant postoperative cyclophosphamide, methotrexate and fluorouracil administration used for breast cancer treatment, should not be reduced because of obesity [27]. Indeed, in this Finnish study, 368 women with localized breast cancer were included between 1987 and 1993. Obese patients did not develop more leukopenia in comparison with non-obese patients with a similar chemotherapy dose calculation [27].

Furthermore, Rosner et al. concluded in another retrospective analysis that dosing chemotherapy according to actual body weight did not induce substantially higher risk of toxicity in patient with stage II, breast cancer but provide a worse prognosis for long-term failure-free survival [20]. All studies cited are summarized in Table 1.

Colon cancer

Colorectal cancer is the third most common cancer worldwide [28], and a disease in which chemotherapy is widely used, either in the adjuvant or advanced disease settings. Dignam et al showed that among colon cancer patients, a BMI greater than 35.0 kg/m^2 at diagnosis was associated with an increased risk for recurrence of and mortality from colon cancer [3].

Table 1. Summarizing studies on body surface area adjustment in obese patients with breast cancer treated with chemotherapy.

	Nature of study	Inclusion criteria	Number of obese patients enrolled	Chemotherapy regimen	Method of BSA adjustement	Percentage of patients with adjusted BSA	Results	Study reference
Breast cancer	Retrospective	BMI $\geq$ 30 Adjuvant chemotherapy	555	Epirubicinx3 +paclitaxelx3+cyclophosphamidex3 (iddETC regimen) or epirubicin + cyclophosphamide + paclitaxel + capecitabine (EC-TX regimen)	Ideal weight or capping to 2m^2	31%	Higher rate of severe toxicities (real BSA)	21
	Retrospective	Early breast cancer	79	Neoadjuvant/adjuvant chemotherapy (FEC-T,FEC,ECaP)	Chemotherapy dose lower than expected	–	Dose capping is associated with lower rate of febrile neutropenia	23
	Retrospective	Non metastatic breast cancer	114	5-fluorouracil + epirubicin + cyclophosphamide followed by docetaxel (FEC-T), or Doxorubicin + cyclophosphamide + docetaxel + trastuzumab(ACTH).	Capped BSA	15.8%	No significant increase toxicities	24
	Retrospective	Adjuvant chemotherapy	108	5-fluorouracil + epirubicin + cyclophosphamide (FEC)	–	–	No significant increase toxicities	25
	Retrospective	Premenopausal patients with node-positive breast cancer	152	(cyclophosphamide, methotrexate and 5-fluorouracil).	Lower chemotherapy dose (85% of expected dose)	39% of patients receive lower chemotherapy doses	No significant increase toxicities Significant worse outcome for the ER-negative cohort	25
	Retrospective	Non metastatic pT1-4 node positive breast cancer	368 (Total population)	CMF regimen (cyclophosphamide, methotrexate	Drug doses were calculated on BSA basis	–	No reduction of chemotherapy doses because of obesity	26
	Retrospective	Stage II breast cancer patients with positive regional lymph nodes	568	Adjuvant cyclophosphamide, doxorubicin, and fluorouracil (CAF)	Actual Body Weight	–	Dosing chemotherapy according to actual body weight did not induce substantially higher risk of toxicity	20

Table 2. Table summarizing studies on body surface area adjustment in obese patients with colon cancer treated with chemotherapy.

Solid tumors	Nature of study	Inclusion criteria	Number of obese patients enrolled	Chemotherapy regimen	Method of BSA adjustement	Percentage of patients with adjusted BSA	Results	Study reference
Colon cancer	Retrospective phase III PETACC 3 trial	Stage III colon cancer	280	Leucovorin 5-FU (LV5FU2) or LV5FU2 plus irinotecan	Dose capping at 2 m2	16,10%	Dose reduction strategy should be avoid in adjuvant treatment of colon cancer	29
	Retrospective	Advanced colorectal cancer	870	Chemotherapy regimen is defined in Focus, Focus2 and coin trials	Dose reduction (5% below)	54%	Do not support the policy of reducing chemotherapy doses for obese patients with colorectal cancer	30
	Retrospective	Stage II and III rectal cancer	306	Chemotherapy regimen is defined in Trial 0114	Actual Body Weight	–	obese patients experience less toxicity associated with adjuvant chemoradiotherapy, suggesting that actual body weight dosing of fluorouracil for obese patients is justified	31
	Retrospective	Women with Stage II–III colon carcinoma	600	Chemotherapy regimen is defined in 0089 treatment trial	–	–	obesity was not associated with any increase in chemotherapy-related toxicity	32

Retrospective analysis from PETTAC 3 study, evaluated the effects of dose reduction in obese stage III colon cancer patients undergoing adjuvant chemotherapy. Survival outcomes and rate toxicities were analyzed in 75 patients under fully weight dose chemotherapy versus 36 patients under doses reduced regimen. Data of this study support that dose reduction strategy should be avoid in adjuvant treatment of colon cancer [29].

Out of the 4781 patients with colon cancer of the retrospective study of Chambers et al, 18% was obese. A comparison of toxicity between obese patients dose reduced and those fully dosed showed no difference (16% versus 17% $p = .71$) [30]. Moreover, the authors of this study suggests that a reduced dose in obese patient leads to a worse progression-free survival [hazard ratio (HR) 1.21, 95% confidence interval (CI) 1.06–1.39, $p = .006$] and a slightly worse overall survival (HR 1.12, 95% CI 0.96–1.30, $p = .152$) [30].

A retrospective study evaluating 1688 patients with stage-II and stage-III rectal cancer under fluorouacil and radiotherapy, showed that increasing BMI in male patient was more likely associated with higher change of local recurrence than normal weight men [HR], 1.61; 95% CI, 1.00 to 2.59). In both gender, overweight and obese patient had lower rate of any grade $\geq$3 toxicities during adjuvant chemotherapy comparing with normal weight individuals. The authors of this study concluded that actual body weight dosing for fluorouacil for obese patient with rectal cancer is justified [31].

The same team published in 2003 a retrospective study conducted within a large cohort of high-risk, Stage-II and Stage-III colon carcinoma patients. In contrast with rectal cancer, obese women with colon cancer experienced significantly worse overall mortality [HR], 1.34; 95% CI, 1.07 to 1.67) and a nonsignificant increase in the risk of disease. Higher BMI in men and women with colon cancer was related with lower rates of any grade 3 to 4 toxicities. The study concluded that the obesity was not associated with any increase in chemotherapy-related toxicity; however, no correlation between regimen type of chemotherapy administration and toxicities rates was noticed in this study [32]. All studies focusing on chemotherapy administration in digestive cancer are summarized in Table 2.

Ovarian and endometrial cancers

A retrospective study conducted in patients with gynecologic malignancy with an objective to compare toxicities and dose modifications between women with a BSA $\geq$ 2 m^2 on uncapped versus capped adjuvant chemotherapy administration. This study identified 59 patients with only 9 patients who received paclitaxel capped at a BSA of 2 m^2. No statistical significant differences in rates of toxicity or dose modification were observed between the two groups [33]. Likewise, descriptive Au-Yeung et al study with 333 overweight and obese patients concluded that dose reduction of carboplatin administration was more common in obese patients and may impact the Progression Free Survival in patients with advanced ovarian cancer [34]

Data of 75 patients treated with chemotherapy for gynecologic malignancy were analyzed retrospectively. No increase in hematological and nonhematological toxicities in obese patients receiving actual weight-based chemotherapy [35].

Another retrospective analysis of 387 patients treated with carboplatin and paclitaxel on Gynecologic Oncology Group (GOG) protocol 158 was performed. In this study, patients were stratified into three groups according to their BMI: normal weight overweight, and obese. The authors concluded that obese ovarian cancer patients had less toxicity than normal weight patients and have suggest that the decrease of toxicities rate may be explain by the substandard drug dose received by obese women [36].

Retrospective analyses of the Scottish Randomized Trial in Ovarian Cancer including 1067 patients. Patients received first-line carboplatin/taxane chemotherapy and were assigned according to their BMI in one of the four groups:

underweight, ideal weight, over weight and obese. All patients received accurate weight-based chemotherapy. No statistical difference was observed in PFS and OS between groups. The obese patients with epithelial ovarian cancer receiving full dose of chemotherapy did not have a poorer prognosis [37]. All cited studies are summarized in Table 3.

Lung cancer

The aim of the only retrospective study in patients with small cell lung cancer was to determine if the administration of chemotherapy to obese patients on the basis of their actual body weight was correlated with an increase in treatment-related toxicity. The authors reported that no support for empiric chemotherapy dose reductions based on ideal body weight is justified for obese patient [38] (Table 4).

Prostate cancer

Little is known about the impact of body composition on clinical benefits of specific therapies for prostate cancer and others genitourinary cancers. A retrospective study of 333 patients with castration metastatic prostate cancer treated with docetaxel was conducted between 2004 and 2012. This study observed secondarily that 34.5% of patients had a significant dose reduction of 10% or higher at treatment initiation. Interestingly, 35% of the population in this study had a BMI higher than 30. Being obese in this study was

Table 3. Table summarizing studies on body surface area adjustment in obese patients with ovarian and endometrial cancers treated with chemotherapy.

Solid tumors	Nature of study	Inclusion criteria	Number of obese patients enrolled	Chemotherapy regimen	Method of BSA adjustment	Percentage of patients with adjusted BSA	Results	Study reference
Ovarian and endometrial cancers	Retrospective	Endometrial and ovarian cancer	59	Paclitaxel and carboplatin	Dose capping at 2 m2	15%	No statistically significant differences in rates of toxicity or dose modification	33
	Retrospective	FIGO Stage III/IV serous ovarian cancer	70	Carboplatin AUC 5 and paclitaxel	Dose reduction (5% below)	66%	Reduced doses may impact on PFS in patients with advanced serous ovarian cancer.	34
	Retrospective	Gynecologic malignancy	75	Gemcitabine, liposomal doxorubicin and paclitaxel	Dose capping at 2 m2	–	Gynecologic cancer patients with BSA $\geq$2m2 treatedwithWB chemotherapy had no increase in hematologic or non-hematologic toxicities when compared to controls	35
	Retrospective	Epithelial ovarian cancer	70	Cisplatin and paclitaxel or carboplatin in combination with paclitaxel	–	–	Obese ovarian cancer patients treated with carboplatin experience substantially less toxicity than normal weight women. The lower toxicity suggests that obese patients may be receiving a substandard drug dose	36
	Retrospective	Ovarian cancer	129	Docetaxel/carboplatin or Paclitaxel/carboplatin	–	0%	Obese patients with epithelial ovarian cancer do not have a poorer prognosis, provided that they receive optimal doses of chemotherapy based on measured GFR and actual body weight	37

Table 4. Table summarizing studies on body surface area adjustment in obese patients with lung cancer treated with chemotherapy.

Solid tumors	Nature of study	Inclusion criteria	Number of obese patients enrolled	Chemotherapy regimen	Method of BSA adjustement	Percentage of patients with adjusted BSA	Results	Study reference
Lung cancer	Retrospective	Small-cell lung cancer	262 (Total patients)	Cyclophosphamide-based regimen or etoposide and cisplatin plus twice-daily chest radiotherapy.	Actual body weight	–	Obesity at the start of treatment was not associated with increased toxicity from treatment or a shortened survival. No support for empiric chemotherapy dose reductions based on ideal body weight was evident from this study.	38

Table 5. Table summarizing studies on body surface area adjustment in obese patients with prostate cancer treated with chemotherapy.

Solid tumors	Nature of study	Inclusion criteria	Number of obese patients enrolled	Chemotherapy regimen	Method of BSA adjustement	Percentage of patients with adjusted BSA	Results	Study reference
castration-resistant metastatic prostate cancer	Retrospective	Metastatic disease at the time of initiation of docetaxel chemotherapy	118	Docetaxel administered intravenously every 3 weeks, or weekly in the break week(s)	Discretion of the treating oncologist	34.5% (reduced doses)	Empirical dose reduction is this population is not warranted	39

associated with fewer side effects, which was probably due to reduced docetaxel doses. The authors concluded that empirical dose reduction is this population is not warranted [39] (Table 5).

Other types of malignancies

A retrospective study was conducted in patients with Diffuse Large B-Cell Lymphoma (DLBCL). In this curable disease, relative dose intensity is associated with treatment efficiency. Out of 1384 patients included in this study, 119 patients had BSA $\geq$ 2.1 m^2 and received a capped dose of doxorubicin and 33 patients had the same BSA and received a full weight dose of doxorubicin. This study did not show any impact of doxorubicin dose capping on PFS nor OS in DLBCL patients. The data of this study suggest that both therapeutic options (capping and uncapping) seem acceptable in DLBCL patients with elevated BSA [40].

Chemotherapy dose capping in obese patient (BSA $\geq$ 2.15 m^2) with acute myeloid leukemia was associated with worse overall survival at 5 years and displayed a worse adverse outcome. Data of this study suggest that full doses in patients with very high BSA and eligible to intensive therapy must be administrated [41]. On the contrary, chemotherapy capping dose at m^2 was well tolerated in 233 obese patients intensively treated for acute myeloid leukemia. Capping strategy in this study was not associated with poorer in this population [42].

The effect of obesity on optimal chemotherapy dosing for obese patients with multiple myeloma was also evaluated in retrospective study. Patients were treated with high dose of melphalan, with or without total body irradiation (TBI). Medical records of 1087 patients were analyzed. 18% of patients present obesity, while 11% of patients had a severe obesity. Reduced doses of melphalan were given to 78% of severely obese, 56% of obese without any evidence of an effect of dose reduction on PFS. This strategy of reducing melphalan doses did not impaired clinical outcomes of obese patients [43].

A retrospective study was conducted comparing obese patients (body mass index [BMI] _ 30 kg/m^2) receiving capped chemotherapy doses at a BSA of 2.2 m^2 with nonobese (BMI _ 25 kg/m^2) patients with lung, colorectal, or hormone-refractory prostate cancer. Overall, obese patients with capped dosing experienced a lower incidence of severe myelosuppression and tolerated more cycles of chemotherapy compared with nonobese patients [44].

Severe chemotherapy-related toxicity was evaluated prospectively in 606 patients with solid tumors during the first three cycles of treatment. In this study, chemotherapy dose administration in obese patients was calculated according to actual body weight and seems to be relatively safe. Indeed, there were no significant differences of severe toxicities rate between genders, type of cancer, or between the different chemotherapy regimens [45].

Finally, the meta-analysis of Hourdequin analyzed toxicities rate and survival outcomes between obese and normal weight of patient with any type of cancer receiving chemotherapy. Inclusion criteria were respected in 12 studies representing 9314 patients. This meta-analysis demonstrates that no statistical difference was observed in terms of toxicities rate and survival outcomes between obese patients receiving chemotherapy based on actual body weight and normal weight patients [46].

Discussion

The prevalence of obesity, defined as body mass index (BMI) $\geq$30 kg/m^2, continues to increase. The worldwide prevalence of obesity has nearly doubled between 1980 and 2008. In 2008, 10% of men and 14% of women in the world were obese (BMI $\geq$ 30 kg/m^2), compared with 5% for men and 8% for women in 1980. Raised body mass index also increases the risk of cancer of the breast, colon, prostate, endometrium, kidney, and gall bladder.

Obesity affects also pharmacokinetic of antineoplastic agents [6]. There are limited available data and clinical trials regarding pharmacokinetic in obese patients. Indeed, pharmacokinetic parameters in obese patients seem to vary inconsistently and are not predictive of efficacy or toxicity to the drug administered. Standardization of an appropriate formula for chemotherapy dosing in these individuals become a clinical challenge, especially knowing that formula of Dubois and Dubois was not validated on obese patient. Indeed, at this time, there is at least eight different methods to estimate body weight for obese patient. None of the formulae gives acceptable estimation for unstandardized populations especially in cancer which population is often over or underweighted, or presenting edema.

More pharmacologic and scientific studies are needed to improve therapeutic management of this growing population. Moreover, many chemotherapy drugs are relatively lipid insoluble and, therefore, distribute poorly into adipose tissue. Obese patients tend to have a greater proportion of fat to total body weight; consequently, the obese patient may theoretically receive a relative overdose of these lipid-insoluble medications.

This review highlights on the fact that the impact of obesity and chemotherapy dosing have been evaluated only in

retrospective studies with conflicting results. Indeed, in breast cancer, while GAIN study concluded that toxicities rate is increased when chemotherapy doses was not reduced [21]. Furthermore, dose capping in obese patients was associated with lower rate of febrile neutropenia in comparison with other groups in Lote et al study [23]. In contrast, four retrospective studies suggested that accurate dosing chemotherapy did not induce a higher risk of toxicities [20,24,25,27]. Contradictory data were reported also for progression free survival and overall survival in this population. The same conflicting results was also observed in acute myeloid leukemia in two retrospective studies realized on the same population with very close inclusion criteria [41,42].

Otherwise, retrospective studies design always evaluated toxicity in obese patients receiving chemotherapy on the basis of actual body weight compared with nonobese patients. Futures studies should be prospectively examine the impact of capping, actual or ideal body weight in obese population. Furthermore, it becomes evident in view of current literature to reconsider chemotherapy methods of calculation in obese patients by an evaluation of sarcopenic obesity (SO) in this population. SO is defined by the coexistence of a severe muscle depletion and high fat mass [47]. Moreover, SO is associated with severe clinical complication, higher incidence of chemotherapy toxicities and higher rate of mortality [48]. Sarcopenic obese patients with esophageal cancer (OC) are at higher risk for developing dose-limiting toxicity during chemotherapy compared to nonsarcopenic OC patients [49]. Obese sarcopenia must be considered for stratification of patient's included in future clinical trials.

Moreover, no study had analyzed the impact of BSA adjustment on chemotherapy toxicities occurrence by gender. Chambers et al study, observed that among 18% of men ($N = 578$) and 15% of women ($N = 248$), 17% and 20% have experienced respectively significant grade 3 or 4 toxicity [30]. An exploratory analysis of PETACC 3 study showed that dose reduction adversely affected Relapse Free Survival (RFS) and Overall Survival (OS) mainly in men but not in women patients[29]. It appears that there is no effect of body surface area ajustement on chemotherapy outcomes by gender. More clinical trials are needed to clarify this question.

In conclusion, based on this review, only a single study was pointing toward increased of global toxicities of full weight dosing [21]. Furthermore, ASCO recommends using full weight dosing when treating obese cancer patients with chemotherapy [18]. Prospective clinical trial are crucial to clarify conflicting results highlighted in this review and to standardize chemotherapy administration in this population. Moreover, more pharmacological studies are needed to understand the pharmacokinetics of antineoplastic agents in this population. Finally, the exploitation of computerized tomography images for the determination of body composition must be required before chemotherapy initiation.

Disclosure statement

The authors declare that they have no conflict of interest

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