DOSING OF PLATINUM AND TAXANES IN OBESE PATIENTS: A SYSTEMATIC REVIEW

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Introduction

Platinum and taxane-based chemotherapy dosing, as others anticancer agents, is based on body surface area (BSA), except in the case of carboplatin that is more often based on the area under curve (AUC). Both parameters depend on the weight, and the obesity (body mass index-BMI≥30kg/m2) could lead to overdose. Some guidelines recommend using actual body weight (ABW) in this patients avoiding arbitrary dose-reductions that can compromise efficacy. Therefore this issue remains a challenge.

Obese patient

Chemotherapy Dosing

Based on BSA or AUC (carboplatin)

Some guidelines recommend:
- Use ABW
- Avoid arbitrary dose-reductions

If we use ABW, Overdose?

Risk of toxicity

Abbreviations
- ABW, actual body weight
- AUC, area under the curve
- BMI, body mass index
- BSA, body surface area

Objective

To analyze the evidence and recommendations available about the dosage of platinum-based (cisplatin, carboplatin, oxaliplatin) and taxane-based (paclitaxel, docetaxel, nab-paclitaxel) chemotherapy regimens in obese patients.

Methods

A formal literature search was performed for each chemotherapy drug on three databases: Pubmed, Scopus and Web of Science (WoS). The following strategies were used:

Eventually we limited the search by language (English/Spanish).

- Pubmed → ((obese [Title] OR obesity[Title])) AND drug[Title/Abstract]
- Scopus → (obese or obesity) AND TITLE-ABS-KEY (drug)
- WoS → TITLE: (obese or obesity) AND TOPIC: (drug)

Exclusion criteria:
(A) Not useful or incomplete information for the aim of the study
(B) Insufficient simple size (Total n<10, Subgroup n<5)
(C) Obesity criteria ≠ IMC≥30 kg/m²
(D) Systematic review
(E) Full-Text no available

Inclusion criteria:
Use of ABW in obese patients and analysis of toxicity and/or efficacy

Results and Discussion

CISPLATIN — 36 articles

33 articles excluded: (A) 19 articles, (C) 5 articles, (D) 8 articles, (E) 1 article.

3 articles included	**Pharmacokinetics**	Drug clearance is increased. AUC ratio in obese patients and lean controls is closer to one when dosing using ABW. Dose adjustments in obese patients is discouraged. (Sparreboom 2007).
	Efficacy and toxicity	Similar efficacy and toxicity using actual BSA across BMI in patients with metastatic urothelial disease. (Leiter 2016).
		No consistent associations of significance between increased BMI and increased toxicity. No statistically significant differences in survival. No dose adjustments are justified. (Georgiadis 1995).

CISPLATIN
Use ABW. Increased clearance and volume of distribution

CARBOPLATIN — 58 articles

53 articles excluded: (A) 20 articles, (B) 1 article, (C) 9 articles, (D) 11 articles, (E) 12 articles.

5 articles included	**Pharmacokinetics**	Use adjusted body weight (BW) to estimate clearance with Cockcroft-Gault equation and use Calvert formula for dosing. (Nelson 2012, Ekhart 2009).
		Design of a new formula for clearance estimation in underweight, normal-weight and obese using ABW, cystatin C, creatinine, age and sex. (Schmitt 2009).
		Consider ABW for dosing chemotherapy in obesity. Dose adjustments in obese patients is discouraged. Drug clearance is similar between obese and normal-weight patients. (Sparreboom 2007).
	Efficacy and toxicity	No significant evidence of increased toxicity among obese women with either full or adjusted chemotherapy doses. Full BSA based-dosing appears to be tolerated as well in obese as in lean women (Carrol 2014).

CARBOPLATIN
Calvert formula for dosing. Estimation of GFR using ABW or adjusted BW; limit GFR to a maximum of 150 mL/min

OXALIPLATIN — 17 articles

16 articles excluded: (A) 11 articles , (B) 1 articles , (C) 2 articles , (D) 2 articles.

1 article included	**Efficacy and toxicity**	No more toxicity in fully-dosed patients. No less toxicity in dose-reduced patients. Worse progression-free survival in dose-reduced patients. (Chambers 2012).

OXALIPLATIN
Use ABW. Monitor neurotoxicity

PACLITAXEL — 43 articles

41 articles excluded: (A) 25 articles, (B) 4 articles, (C) 3 articles, (D) 7 articles, (E) 2 articles.

2 articles included	**Pharmacokinetics**	Drug clearance is increased in obese patients. Consider ABW for dosing in obesity. Dose adjustments in obese patients is discouraged. (Sparreboom 2007).
	Efficacy and toxicity	More neuropathy and less grade 4 neutropenia and neutropenic fever observed in obese patients compared to no obese (Sparano 2012).

PACLITAXEL
Use ABW

DOCETAXEL — 40 articles

33 articles excluded: (A) 22 articles, (B) 1 articles (C) 2 articles, (D) 6 articles, (E) 3 articles.

6 articles included	**Pharmacokinetics**	The use of ABW in the formula for BSA for dosing resulted in statistically significantly increased exposure in the obese, especially in women (Sparreboom 2007).
	Efficacy and toxicity	Obese women receiving full uncapped doses have increased pathological complete response and favorable progression-free survival (Farr 2017). No differences in efficacy between obese and non obese in the rest of the articles. (Ladoire 2013, Carroll 2014)
		More neuropathy and less grade 4 neutropenia and neutropenic fever in obese patients compared to non obese (Sparano 2012). No difference in toxicity in the other articles but the obese tend to present more toxicity. (Carroll 2014, Farr 2017). More hematologic toxicity using actual BSA across BMI in obese patients. (Furnaletto 2017).

DOCETAXEL
Use ABW

SARCOPENIC OBESE
More toxicity observed

Nab-paclitaxel: None articles were found.

Exclusion criteria:

Although many articles were excluded, some of them present an interesting approach or complementary information about chemotherapy dosing in obese patients:

(C)
- Palmela 2007 and Anandavadivelan 2016 analyze the effect of body composition in addition to BMI. Higher risk of toxicity was found in sarcopenic patients compared to non-sarcopenic obese patients.

(C)
- Stocker 2016 suggests more neuropathic toxicity in patients receiving full-dose vs reduced-dose of oxaliplatin across all BMI subgroups.

(D)
- Hourdequin 2013 (meta-analysis) observe that obese patients receiving chemotherapy based on ABW experience similar or lower rates of toxic effects compared with normal-weight patients, and survival outcomes do not differ.

(B)
- Miyahara 2013 show significant differences in grade 3/4 hematological toxicity in obese patients with solid tumors in the ABW and ideal BW, but not in obese patients with hematological malignancies. In solid tumor patients with complications, incidence of Grade 4 hematological toxicity was significantly higher in the ABW than in the ideal BW.

Conclusions

For platinum and taxane-based chemotherapy the use of ABW for dosing in obese patients is the most accepted proposal according to the analyzed literature.

For carboplatin, depending of the GFR obtained, this should be limited to a maximum of 150 mL/min or use an adjusted body weight for dosing.

Furthermore, analysis of body composition could be used for dosing or reducing risk of toxicity in sarcopenic patients.