ANTHRACYCLINE DOSING IN OBESE ADULT PATIENTS: A SYSTEMATIC REVIEW

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eahp european association of hospital pharmacists
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Background and importance

Chemotherapy dosing for obese patients (body mass index [BMI]≥30Kg/m2], remains undefined. Most recent publications discourage arbitrary dose-reductions that can compromise efficacy. However, because of anthracyclines dose-dependent cardiotoxicity and also inherent obesity-related cardiovascular risk factors is advisable to review the evidence available of toxicity in this population.

Obese patient

Chemotherapy Dosing
Anthracyclines

Based on Body Surface Area (BSA)

Recent publications recommend:
- Arbitrary dose-reductions

If arbitrary dose-reductions, Efficacy?

Risk of dose dependent toxicity with BSA calculated with Actual Body Weight (ABW)

Aim and objectives

To define the most adequate dose strategy for anthracyclines in obese adult patients based on efficacy and toxicity results and/or pharmacokinetic data.

Methods

We conducted a systematic review in Pubmed, Scopus and Web of Science using predefined keywords [(obese or obesity) and (daunorubicin or doxorubicin or epirubicin or idarubicin)]. We excluded paediatric and non-English papers. Moreover, we looked at studies with relevant information about safety and efficacy.

- 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
(F) Pediatric population

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

Results and Discussion

DOXORUBICIN
97 articles

87 articles excluded: (A) 71 articles, (B) 3 articles, (C) 8 articles, (D) 1 article, (E) 4 articles, (F) 10 articles.

10 articles included	**Pharmacokinetics**	Area under the concentration-time curve (AUC) for doxorubicin in the severely obese patients was significantly greater than in normal bodyweight patients and the CL was significantly smaller. (Rodvold 1988)
		Drug clearance was reduced and AUC was increased in obese patients but with no statistical significant differences (Sparreboom 2007).
	Efficacy and toxicity	Dose based on BSA without adjustments in Triple-Negative Breast Cancer obesity was associated with worse event-free survival. (Liu 2018)
		Obesity was an important independent prognostic factor which has an adverse effect on pathological complete response. (Karatas 2017)
		Full uncapped doses of R-CHOP chemotherapy administered to obese patients with non-Hodgkin lymphoma are safe, well tolerated, and do not lead to inferior treatment response or long-term outcomes. (Chan 2016)
		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)
		Severe obesity (BMI ≥ 35) with capped and uncapped doses had a significantly increased risk of recurrence compared to reference group. (Bella Pajares 2013)
		During uncapped doses obese patients exhibited less grade 4 neutropenia and more 3 and 4 grade cardiac toxicity but similar en febrile neutropenia, infection and overall cardiac toxicity. (Sparano 2012)
		Administration of initial and overall full weight-based doses of adjuvant chemotherapy in overweight and obese women is likely to improve outcomes in this group of patients. (Griggs 2015)
		Cardiovascular risk increase when increasing BMI but could not establish if it was due to the use of full doses or to the obesity itself. (Guenancia 2016)

DOXORUBICIN
Data not consistent

EPIRUBICIN
26 articles

22 articles excluded: (A) 17 articles, (B) 1 article, (D) 3 articles, (F) 1 article.

4 articles included	**Efficacy and toxicity**	Obese women receiving full uncapped doses of anthracycline-taxane-based NAC have increased pCR and favorable progression-free survival. This could result from increased dose intensity with increased efficacy and toxicity. (Farr 2017)
		Obese patients receiving dose dense chemotherapy according to their real BSA have a higher risk of developing severe toxicities without influencing survival. Therefore, a dose adjustment of intense dd chemotherapy should be carried out to avoid life-threatening complications. (Furnaletto 2016)
		Obesity has no impact on breast cancer prognosis when modern adjuvant chemotherapy, at the appropriate dose intensity, is delivered. (Ladoire 2014)
		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)

EPIRUBICIN
Data not consistent

IDARUBICIN
9 articles

7 articles excluded: (A) 4 articles, (F) 3 articles.

2 articles included	**Efficacy and toxicity**	Did not find any significant impact of obesity on outcome in the whole series. Dose optimization are needed in the ELN favorable subgroup since dose capping may be deleterious. (Taritian 2016)
		Age≥60, unfavorable karyotype, secondary AML, and positive smoking status had adverse impact on overall survival in a multivariate analysis, while BMI did not. (Lee 2011)

IDARUBICIN
Data not consistent

DAUNORUBICIN
14 articles

13 articles excluded: (A) 9 articles , (F) 4 articles.

1 article included	**Efficacy and toxicity**	Obesity was not an independent prognostic factor of outcome or toxicity. Empiric dose reductions based on obesity did not result is significantly different complete remission rates. (Lin 2013)

DAUNORUBICIN
Data not consistent

Conclusions

Even that literature regarding safety and efficacy is not consistent; since there is better response with full anthracycline doses and toxicity can be monitored, dose reduction in obese patients is not recommended. However, presence of other comorbidities may be a reason for dose reduction.