

## London Cancer Guideline- Dosing in Obesity

### 1. Introduction

Chemotherapy dosing in patients has historically been based on body surface area (BSA). (Freireich, 1966) Overweight and large patients have often been treated with a BSA calculated using the patient's ideal or adjusted bodyweight or the patient's BSA would be capped (often at  $2\text{m}^2$ ). (Griggs, 2008) Despite widespread use of dose capping, the studies underpinning the concept used very small numbers of patients and the differences in pharmacokinetics (between normal and obese patients) were difficult to identify and characterise. (Wong, 2014)

The American Society of Clinical Oncology (ASCO) addressed the problem by publishing a guideline. (Griggs, et al., 2012) The content of this guideline is the basis for most of the guidance below. There is evidence that not dosing patients at the full intensity and dose reducing the chemotherapy affects the overall survival of patients in the curative treatment setting. (Bonnetterre, 2005) (Budman, 1998) (Frei, 1980) (Lepage, et al., 1993) (Lyman, 2006) (Wong, 2014) Also the toxicity concerns regarding dosing patients at full unadjusted doses are unfounded.

Dosing for Haematopoietic Stem Cell Conditioning has also been covered in this guideline using the ASBMT guideline from 2014.

For adults, overweight and obesity ranges are determined by using weight and height to calculate BMI.

An adult who has a BMI between 25 and  $29.9\text{ kg/m}^2$  is considered overweight; an adult who has a BMI of  $\geq 30\text{ kg/m}^2$  is considered obese; an adult who has a BMI  $\geq 40\text{ kg/m}^2$  (or  $\geq 35\text{ kg/m}^2$  with co-morbid conditions) is considered morbidly obese.

### 2. Scope

The purpose of this guideline is to summarise the ASCO guidance produced in 2012 on this issue. At the end of the guideline is list of references which have been published since 2012 when the guideline was published.

The ASCO guideline does not cover the use of cytotoxics/agents in haematopoietic stem cell conditioning. A different source guideline from the ASBMT has been used for the guidance regarding dosing in BMT.

Please consult the ASCO guidance and the ASBMT guideline to review the data summary which has been used to make the recommendations summarised below. The guideline does not replace individual clinical judgement and clinicians may have good grounds for deviating from this guideline.

### **3. Guidance-** Excludes Haematopoietic Stem Cell Transplant Conditioning and Paediatrics

#### **3.1 -Obese Patients being treated with curative intent**

##### **3.1.1 Actual body weight should be used to calculate BSA for cytotoxic chemotherapy dose calculations regardless of obesity status.**

###### **Evidence for this:**

There is no evidence that short- or long-term toxicity is increased among obese patients receiving chemotherapy doses based on full weight based doses to calculate BSA and use that BSA value to calculate the dose of chemotherapy.

The clinical data indicates that myelosuppression is the same or less pronounced among the obese than the non-obese when administered full weight-based doses.

For certain a tumour types there is evidence (e.g. in breast) that the efficacy of treatment is compromised if obese patients are not dosed according to actual body weight to calculate BSA and dose of that BSA value. The data indicates poorer disease free survival and overall survival rates.

Data in other malignancies than breast is more limited but a dose-response relationship has been shown to exist for many other malignancies.

##### **3.1.2 Clinicians should follow the same guidelines for dose reduction, regardless of obesity status, for all patients, depending on the type and severity of toxicity, and any comorbid conditions for patients being treated to curative intent.**

###### **Evidence for this:**

The evidence does not indicate the need for greater dose reductions in obese patients compared to non-obese patients.

The aim is to reverse any dose applied because of renal/hepatic dysfunction once the renal or hepatic function resolves and then dose the patient at full dose if appropriate.

##### **3.1.3 Fixed doses of chemotherapy should only be used for certain chemotherapy agents e.g. bleomycin 30,000 IU or vincristine at max dose of 2mg due to neuropathy concerns.**

###### **Evidence for this:**

Evidence is available for selected agents e.g. vincristine, bleomycin in BEP, carboplatin dosing based upon renal function and dosing calculated on AUC using standard formulae.

##### **3.1.4 Currently Pharmacokinetics or pharmacogenetic factors cannot be taken into account when recommending dosing for obese patients.**

**Evidence for this:**

There is little good trial evidence (due to a lack of statistical power) about the effect of obesity on the pharmacokinetics of chemotherapy agents. It is thought that the volume of distribution of agents and the clearance of agents is different in obese patients compared to the non-obese.

Trial eligibility restrictions from the outset in clinical trials often include as many patients as possible and there is a lack of pharmacokinetic analyses performed in trials and a lack of analysis for the obese subpopulation.

**3.2 -Obese Patients being treated with palliative intent****3.2.1 The same guidance above applies for palliative intent patients as for curative, however the further points below also need to be considered.**

Dose reductions are often applied to palliative intent patients more readily than curative patients. The same guidelines apply for obese patients as non-obese patients.(Griggs, 2008)

The reduced efficacy of dosing using adjusted weight on disease free survival/overall survival was shown in the literature from patients who were being treated for early stage disease with curative intent. Therefore there is more limited evidence for treating obese patients at full weight doses in advanced disease where there is palliative treatment intent.

**4. Guidance for Obese patients undergoing High Dose Therapy with Autologous Stem Cell Support or Allogeneic BMT Conditioning**

The guidance below is based upon the *“ASBMT Guideline Conditioning Chemotherapy Dose Adjustment in Obese Patients: A Review and Position Statement by the American Society for Blood and Marrow Transplantation Practice Guideline Committee”*.

**The table below summarises the dosing recommendations for Haematopoietic Cell Transplant Conditioning Agents in the Obese Individual:**

Agent	Suggested Dosing	Additional Information
Alemtuzumab	Flat dosing in adults based upon regimen selected	Addition of this agent to conditioning regimens continues to evolve and there are currently no data on dose adjustments for obese individuals.
Busulfan	Dose on ABW25 in adults (obese and nonobese) receiving per kilogram dosing or BSA based on TBW for m <sup>2</sup> dosing. All regimens >12 mg/kg PO equivalent are recommended to have PK targeting as appropriate for the disease state. Regimens using doses ≤12 mg/kg PO equivalent do not have sufficient information to recommend routine PK monitoring at this time. Paediatrics should be dosed upon TBW with similar monitoring guidelines.	PK monitoring has reduced SOS/VOD from an occurrence rate of approximately 20% to less than 5% [35]. AUC/Css targeting varies by regimen. For BuCy regimens the MTD is 16 mg/kg PO equivalent over 4 d for adults. For BuFlu and BuFluAlemtuzumab MTD based upon daily AUC have been determined. Dosing with other combinations of agents is still being determined.
Carboplatin	Dose adults on BSA based on TBW.	No current literature consensus for dosing carboplatin based on AUC for HCT regimens or adjustments on dosing during HCT for obese individuals.
Carmustine	Dose adults on BSA based on TBW unless >120% IBW then dose on BSA based on ABW25.	Pulmonary toxicity >50% at 600 mg/m <sup>2</sup> with multiple agent regimens. MTD of 1200 mg/m <sup>2</sup> as single agent with 9.5% pulmonary toxicity.
Clofarabine	Dose adults and children on BSA based on TBW.	Addition of this agent to conditioning regimens continues to evolve and there are currently no data on dose adjustments for obese individuals.
Cyclophosphamide	Dose on the lesser of TBW or IBW for Cy200. For Cy120 dosing can be either IBW or TBW until >120% IBW then dose based on ABW25. The former method is preferred for adults and the latter is preferred in paediatrics.	
Cytarabine	Dose adults and children on BSA based on TBW.	Cytarabine dosing generally lower than dose used in leukaemia consolidation regimens.
Etoposide	Dose adults on ABW25 for mg/kg dosing and BSA based on TBW for BSA based dosing.	DLT of mucositis.
Fludarabine	Dose adults on BSA based on TBW.	Risk factors and effects of chemotherapy on post treatment leukoencephalopathy still being studied for conditioning regimen doses above 125 mg/m <sup>2</sup> .
Melphalan	Dose adults on BSA based on TBW.	DLT of mucositis. Adjustments for age and renal function are still not standardized.
Pentostatin	Dose adults on BSA based on TBW.	Addition of this agent to conditioning regimens continues to evolve and there is currently no data on dose adjustments for obese individuals.
Thiotepa	Dose adults on BSA based on TBW unless >120% IBW then dose on BSA based on ABW40.	Multi-agent MTD is 500-750 mg/m <sup>2</sup> , single-agent MTD is 900 mg/m <sup>2</sup>
Antithymocyte globulin - equine	Dose on mg/kg based on TBW.	Addition of this agent to conditioning regimens continues to evolve and there are currently no data on dose adjustments for obese individuals.
Antithymocyte globulin - rabbit	Dose on mg/kg based on TBW.	Addition of this agent to conditioning regimens continues to evolve and there are currently no data on dose adjustments for obese individuals.

**ABW25** = IBW + 0.25(TBW-IBW); **ABW40** =IBW +0.4(TBW-IBW); **AUC**, area under the curve; **Bu**, busulfan; **BMI**, body mass index; **BSA**, body surface area; **Css**, concentration at steady state; **Cy**, cyclophosphamide; **Cy120**,cyclophosphamide 120 mg/kg; **Cy200**, cyclophosphamide 200 mg/kg; **DLT**, dose-limiting toxicity; **Flu**,

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Fludarabine; **MTD**, maximum tolerated dose; **PK**, pharmacokinetics; **PO**, oral; **SOS**, sinusoidal obstruction syndrome; **TBW**, Total or actual body weight; **VOD**, veno-occlusive disease. **IBW** For Males:  $IBW = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet}$ . For Females:  $IBW = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet}$

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