Special article

Conditioning regimen dosing calculation for patients with obesity undergoing hematopoietic stem cell transplantation

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Introduction

Chemotherapy dosing among patients undergoing HSCT is essential for successful clinical outcomes. Either incidence of treatment success or complications depends on optimum dosing. Higher doses have been associated with higher toxicity while lower doses can lead to treatment failure. Bodyweight plays an important role in dose calculation and optimization for transplant candidates and should be normalized carefully and properly. The effects of pharmacokinetic alterations especially distribution and elimination among obese individuals are the main concerns for dosing consideration and remain difficult to predict. Currently, the prevalence of overweight and obese individuals has been gradually increasing over the past decade. However, the most proper weight for chemotherapy dosing for HSCT has been uncleared. Many strategies to normalize body weight have been studied and used in clinical practice; nevertheless, optimal weight for dose calculation remains varied. This article aims to review the effects of pharmacokinetic alteration among obese individuals, the association between chemotherapy dosing in obesity and clinical outcome, and body weight normalization and chemotherapy dose calculation including guideline recommendations.

Obesity incidence and classification

Overweight and obesity have been defined based on body mass index (BMI), where height and weight are used for calculation. The prevalence of obesity has approximately doubled since 1980 worldwide and become a public health problem representing a crucial risk factor for global deaths.

In Thailand, obesity epidemics have been increasing consistently. The result from a study in 2011[1] revealed the prevalence of obese individuals among Thai citizens compared with another study in 2020[2] demonstrated the prevalence of obesity (BMI > 25 kg/m^2) was 33.9% in 2012 and 44.8% in 2018 ($p < 0.001$). Furthermore, the study revealed the factors related to obesity included higher age, smoking, instant coffee drinking > 1 cup weekly, a higher number of chronic diseases, and a higher level of spot serum urine sodium[2]

Obesity and conditioning chemotherapy dosing

The aspect of overweight and obesity not only affects health problems but also becomes a crucial factor to be considered in conditioning chemotherapy dose optimization. The formula for calculating chemotherapy dose both body surface area (BSA) and weight-based dose are based on individual body weight. Some pharmacokinetic reasons are explaining dose-related toxicity of chemotherapy and obesity associated with metabolism and elimination alteration or dysregulation of cytotoxic agents among patients with obesity[3].

Data are limited concerning pharmacokinetics (PK) in patients with obese status. This may be due to pharmacokinetic analysis in phase 1 clinical trials which often exclude patients with complicated comorbidities which often occur among patients with obese status. The two possible pharmacokinetic components tending to affect a pharmacokinetic alteration among patients with obese status are volume of distribution (Vd) and elimination. The possible pharmacokinetic alteration mechanisms are concluded in Table 2.[4-6]

Table 1 Prevalence of obesity in Thailand[1, 2]

Study	Jitnarin N., et al. (2011)[1]		Sakboonyarat B., et al. (2020)[2]	
Classification	WHO	WPRO	WPRO (2012)	WPRO (2018)
Overweight	19.0% BMI 25.0-29.9 kg/m^2	17.1% BMI 23.0-24.9 kg/m^2	-	-
Class I Obesity	4.0% BMI > 30.0 kg/m^2	19.0% BMI 25.0-29.0 kg/m^2	-	-
Class II Obesity	0.8% BMI > 35.0 kg/m^2	4.8% BMI > 30.0 kg/m^2	-	-
Class III Obesity	0.1% BMI > 40.0 kg/m^2	-	-	-
Overall	23.9%	40.9%	33.9%	44.8%

Table 2 Possible pharmacokinetic alteration mechanisms

Absorption	Distribution	Metabolism	Elimination
Increase in drug bioavailability due to increased gastric emptying time and gut perfusion	Increase in Vd for lipophilic drugs	Hepatic clearance may be altered due to an alteration of liver blood flow	Drug elimination may be decreased due to an accumulation of fat in the liver altering liver blood flow and decreasing drug metabolism
Decrease in subcutaneous drug bioavailability due to alteration of blood flow in adipose tissue	Vd may be decreased due to a decrease of tissue perfusion and % lean mass	CYP450 metabolism alteration due to liver abnormality	Kidney clearance may be altered in inconsistent directions.

Associations have been confirmed between increasing BMI and a significant increase in both incidence and mortality rate for nonHodgkin's lymphoma, leukemia, multiple myeloma, colorectal cancer in premenopausal women, endometrial cancer, breast cancer in postmenopausal women, adenocarcinoma of the esophagus, pancreatic cancer, kidney cancer, ovarian cancer and all cancers combined.[7]

One of the contributing factors thought to be associated with increased mortality among patients with obese status and cancer is chemotherapy underdosing. Currently, BSA has been used to optimize chemotherapy dose based on data from clinical trials extrapolated and applied to chemotherapy dosing to explore dose-limiting toxicity (DLT) and maximum tolerated dose (MTD).

HSCT and conditioning regimen

Hematopoietic stem cell transplant (HSCT) involving the administration of healthy hematopoietic stem cells among patients with bone marrow failure both dysfunction or bone marrow depletion is counted as a lifesaving treatment for both malignant and nonmalignant diseases for many purposes such as reducing tumor burden, generating functional cells or modulating immune.[8] Chemotherapy dose intensity in conditioning regimen is critical for HSCT success; however, optimal conditioning chemotherapy dosing is complicated regarding some variabilities including conditioning regimen, patient's fitness, patient body weight, and therapeutic intent and acceptable toxicities.[8]

Table 3 Updated dosing recommendation for hematopoietic stem cell transplantation conditioning regimens among patients with obese status after ASBMT guidelines 2014 release

Chemotherapeutic Agent	Current Recommendation[4]	Additional Data
Busulfan	- Per kilogram dosing: dose on adjusted body weight with 25% (ABW25) - Based upon BSA dose: total body weight (TBW) - Pediatric dose: TBW	Using IBW resulted in subtherapeutic concentrations and worse PFS among patients with obese staff. ABW25 and ABW40 correction factor improved median PFS but not OS among patients with obese status.[19]
Carboplatin	BSA based on TBW	TBW is recommended for GFR calculation for the dose based on AUC[20]. No significant difference was found in effectiveness and toxicity between patients with obese and normal weight status.[21]
Carmustine	- BSA based on TBW - BSA based on ABW 25 if TBW > 120%	50% of pulmonary toxicity occurs at a dose of 600 mg/m^2 with multiagent regimens and 1,200 mg/m^2 as a single agent. A recent study supported the use of TBW.[22]
Clofarabine	BSA based on TBW	No currently updated data on dose adjustment for patients with obese status.
Cyclophosphamide	- Cy120 (120 mg/kg): BSA based on IBW or TBW unless TBW > 120% IBW then BSA based on ABW25 - Cy200 (120 mg/kg): dose on lower TBW or IBW	Evidence is available of using ABW50 among patients with TBW > 150% IBW.[23]
Cytarabine	BSA based on TBW	No evidence is available supporting improvement of neither effectiveness nor toxicity of dose reduction or capped dose at BSA of 2 m^2.[24]
Etoposide	- ABW25% for mg/kg dosing - TBW for BSA based on dosing	Dose limiting mucositis 1,000 mg/m^2/day ×2 [25]
Fludarabine	BSA based on TBW	No currently updated data on dose adjustment for patients with obese status
Melphalan	BSA based on TBW	Mucositis occurs 24% at dose 4.4-6.4 mg/kg[26]. Recent study does not support dose adjustment in obese populations.[27]
Thiotepa	- BSA based on TBW - ABW40 if TBW > 120% IBW	Multi-agent MTD is 500-750 mg/m^2, single-agent MTD is 900 mg/m^2
Antithymoglobulin (ATG): equine and rabbit	Dose on mg/kg based on TBW	No current data on dose adjustment for patients with obese status

TBW = total body weight; IBW = ideal body weight; ABW = adjusted bodyweight; PFS = progression-free survival; OS = overall survival; MTD = maximum tolerated dose

Table 4 Calculation for different dosing methods

IBW	Male: 50 kg +2.3 kg (height-5 feet)
	Female: 45.5 kg +2.3 kg (height-5 feet)
ABW25	IBW + 0.25 x (TBW – IBW)
ABW40	IBW + 0.4 x (TBW – IBW)
ABW50	IBW + 0.5 x (TBW – IBW)

IBW = ideal body weight; TBW = total body weight; ABW = adjusted bodyweight

Patient weight is one of the factors considered in conditioning chemotherapy dosing. Many efforts were made to standardize appropriate dosing to achieve both therapeutic effects and acceptable or manageable side effects. The most frequently used application of dose calculation is based on BSA, body weight, or PK-based formulas to apply for different physical distribution, toxicities, and metabolisms among chemotherapeutic agents. No single parameter has been established for describing the PK of drugs among individuals with obese status. Moreover, achieving targeted blood levels for specific agents is either scarcely validated, promptly available, or both. Furthermore, variations in target exposure required for proper therapeutic outcomes among different patient groups have been noted.

Dose intensity is of importance

Despite the toxicity of chemotherapeutic agents, especially myelosuppression, dose-dependent cytotoxicity is simultaneously manifested against malignant cells together with the normal cells of the bone marrow, hair follicles and gastrointestinal mucosa. Many clinical studies reveal a consistent association between the dose of cytotoxic agents and clinical outcomes.

Using tumor growth kinetics in aiming for "curative" chemotherapy in advanced solid tumors has demonstrated decreased complete remission and reduced cure rate by one-half when chemotherapy dose has been reduced by 20% while high dose intensity showed higher efficacy in reducing tumors in related studies[9]. In hematologic malignancy, dose intensity manifested a consistent relationship between optimal dose intensity and survival benefits for both disease-free survival and overall survival (OS) as seen in many later studies focusing on survival in diffused large B-cell lymphoma.[10-12]

For transplantation settings, a "high dose" conditioning regimen has been traditionally used variously supralethal doses of total body irradiation (TBI) and chemotherapeutic agents with uncorrelated toxicities. Nevertheless, immunologic reaction with donor cells against malignant host cells provided efficacy of HSCT. Despite the lower risk of relapse among patients receiving high dose regimens, reduced-intensity conditioning (RIC) regimens and nonmyeloablative regimens have been developed in selected populations such as the elderly or non-medically fit patients. RIC regimens dose intensity is between high dose and nonmyeloablative regimens characterized by 30% reduction of alkylating agents or TBI, potentially prolonged cytopenia, and need for stem cell support while nonmyeloablative regimens cause lower cytopenia and do not require stem cell rescue[13]. Consequently, current evidence demonstrated and proved the consistent association between chemotherapy dose intensity and clinical outcome, especially survival benefits, risk of relapse and even toxicity.

Chemotherapy dose optimization and real practice

Many attempts used in chemotherapy dose calculation endeavor to standardize dosing in obese populations. BSA is widely used to calculate dosing depending upon individual body weight and height; however, despite using BSA for optimizing chemotherapy dose, efficacy and toxicity vary[3,8,14]. Obesity tends to be associated with increased recurrence of cancer and mortality rate. An interesting aspect is the undertreatment of individuals with overweight and obese status and cancer. The percentage of first cycle dose reduction referring to a dose proportion less than 0.9 compared with the standard dose were given to 11% of patients with overweight status and cancer, 20% of patients with obese status, and 37% of patients with severely obese status. The reasons for chemotherapy dose reduction among

patients with obese status are altering PK and higher incidence of toxicity from the treatment[14]. Consequently, chemotherapy dose optimization can be concluded in that patients with overweight and obese status have been administered undertreatment chemotherapy which would be associated with higher mortality in this group.

Does reducing the dosing less than full weight-based compromise clinical efficacy among individuals with obesity status and cancer?

The relationship between toxicity and obesity is classified as BMI over 27.3 kg/m^2 amng patients with breast cancer receiving adjuvant chemotherapy. No increasing experience of excess first cycle toxicity or worse clinical outcome was noted. Moreover, the evidence suggested full dose chemotherapy demonstrated improving failure-free survival than reduced dose chemotherapeutic agents.[15]

The up-to-date practice of chemotherapy dose adjustment among patients with obese status undergoing HSCT has been investigated. As for data from 27 countries included in the survey, 45 centers have revealed routinely adjusted chemotherapy doses for patients with obese status (80.5%), 16 centers have used actual body weight (ABW), 10 centers have used ideal body weight (IBW), and 16 centers have used IBW plus 25% of the difference between IBW and ABW. Moreover, 44% of all centers capped the dose at 2 m^2 based on BSA, while the remaining did not.[16]

Guideline recommendation

ASCO guideline 2012 recommended that for patients with obese patients with cancer, especially those suspected to be curative individuals, ABW should be used for chemotherapy dose calculation. Also, ASCO guideline 2021 updated the recommendation of using full weight-based cytotoxic chemotherapy doses to treat patients with obese patients. The additional recommendation in the new version guideline is a fully approved dose of immunotherapy and targeted therapy to be administered to patients with obese patients with cancer. Dose modification should be managed in case of occurrence of toxicity as similarly for patients with nonobese status.[17,18]

The review of the American Society for Blood and Marrow Transplantation (ASBMT) practice guidelines 2014 committee found that due to the current low level of evidence-based information, insufficient data are available to conclude the optimal dose for conditioning regimen for obese individuals. Nevertheless, dose adjustment recommendations are available for specific agents for patients with overweight and obese status receiving conditioning chemotherapy.[4]

Conclusion

The incidence of individuals with obese status in the global population and Thailand is rising continuously[1,2]. Obesity is a crucial factor to be considered in chemotherapy dosing among patients with cancer whose dose-intensity of conditioning regimen is the key to success in stem cell transplantation[9-12]. Obesity is a contributing factor to mortality involving comorbidity, variation of plasma drug concentration, underdosing of therapy[5,6], and variation in clinical outcomes[7,8]. Despite the importance of conditioning regimen dose-intensity to survival, chemotherapy dosing is often reduced or capped among patients with obese status which may lead to underdosing and increased risk of recurrence[14].

Dosing of specific chemotherapeutic agents as a conditioning regimen for patients with obese status should be calculated using optimal dosing weight based on guideline recommendations and up-to-date evidence because of different chemical properties and pharmacokinetic profiles. Nevertheless, current data on pharmacokinetic alteration among patients with obese status remains limited regarding some chemotherapeutic agents. Total body weight (TBW) is widely used in BSA-based dosing calculation while dosing per body weight may require dose normalization based upon

evidence from clinical trials[4,19-27]. Consequently, among individuals with obese status receiving conditioning regimen, using optimal dosing weight for chemotherapy dose calculation is essential for the highest benefit of treatment aiming to prolong survival, eradicate the disease, decrease the risk of recurrence, and minimize treatment toxicity.

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