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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

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A B S T R A C T

Hematopoietic stem cell transplantation (HCT) is a potentially life-saving therapy for patients with malignant and nonmalignant disease states. This article reviews the current published literature on the dosing of pharmacologic agents used for HCT preparative regimens with specific focus on the obese patient population. The review found that dose adjustments for obesity have, to date, been based empirically or extrapolated from published data in the nontransplantation patient population. As a result, the Committee determined that clear standards or dosing guidelines are unable to be made for the obese population because Level I and II evidence are unavailable at this time. Instead, the Committee provides a current published literature review to serve as a platform for conditioning agent dose selection in the setting of obesity. A necessary goal should be to encourage future prospective trials in this patient population because further information is needed to enhance our knowledge of the pharmacokinetics and pharmacodynamics of conditioning agents in the setting of obesity.

INTRODUCTION

Over the past 50 years in the United States, the average weight in adults has increased by 11 kg, whereas the average increase in height has approximated only 2 cm [1]. The prevalence of obesity in children and adolescents ages 2 to 19 years has increased from 5% in 1971 to 16.9% in 2010 [2,3]. This has led to an increasing prevalence of high body mass index (BMI) categories that are used by the World Health Organization to define individuals who are "overweight" (BMI 25 to 29.9 kg/m^2), "obese" (BMI $\geq$ 30 to 39.9 kg/m^2), or "severely obese" (BMI $\geq$ 40 kg/m^2) [1]. BMI categories are considered a rough guide because they may not correspond to the same body fat percentage in different individuals. For similar reasons, particularly because of physiological changes that occur during normal development, BMI estimates that are defined using weight divided by height squared are not applicable to children and adolescents. In children and adolescents, Centers for Disease Control and Prevention growth charts are used to determine the corresponding BMI-for-age and sex percentile. Thus, "overweight" corresponds to a BMI $\geq$ 85th percentile and "obese" corresponds to a BMI $\geq$ 95th percentile [4]. Rates of obesity vary by country and ethnicity. In the United States, more than one third of adults (37.5%) and approximately 17% (or 12.5 million) of children and adolescents are obese [5]. Understandably, dosing chemotherapy in obese cancer patients is a common issue.

Chemotherapy used as part of conditioning therapy before hematopoietic stem cell transplantation (HCT) has multiple purposes. In the autologous setting, the goal is primarily to reduce tumor burden, but in the allogeneic setting, there is the additional need for immune modulation to overcome rejection of the new hematopoietic system. Appropriate dosing has been considered critical in the myeloablative conditioning setting because chemotherapy doses were historically increased to levels just below those at which unacceptable rates of fatal side effects occur. Selecting the optimal

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Table 1
Obesity Overviews and Recommendations from the Literature

Outcomes	Basis	Comments	Reference
Overall reviews			
Patients whose admission TBW was 120%-139% greater than their age-adjusted BMI had higher NRM than patients whose TBW was 100%-119% of age-adjusted BMI.	Retrospective review of 473 (72 obese, 32 very obese) consecutive autologous *adult* patients with mixed hematologic malignancies treated between 1988 and 1995 with 7 different regimens. Median follow-up of 2.3 yrs.	*Dosing*: dosed on TBW at admission unless patient was >15 kg above IBW; then they were dosed on adjusted body weight (40%), ABW40. Patients were compared based on their admission TBW versus their age-adjusted BMI, which is a nonstandard measurement system. Age-adjusted BMI was associated with an increased NRM in obese patients. *Conclusion* Dose adjustment in obese autologous HCT patients does not increase risk for disease relapse.	[23]
No differences in OS between normal and obese for any patient group; TRM and relapse risk were greater in the BMI < 18 group, and relapse was significantly less in the obese and morbidly obese groups.	Retrospective review of the CIBMTR database of *adult* patients (autologous 373 with 85 obese, allogeneic MRD 2041, URD 1801, 654 obese overall) with AML treated between 1995 and 2004 with unreported regimens. Compared underweight (BMI < 18), normal (18-25), overweight (>25-30), obese (>30-34), and morbidly obese (≥35). Median follow-up of 51 to 87 mo.	*Dosing*: Basis for dosing not reported. No differences in GVHD between groups. Unable to assess doses used in conditioning regimens or body weight used. *Conclusion* Obese individuals derive benefit from and can be treated safely with HCT.	[24]
Obese patients had equivalent (NS) OS and PFS but higher infection rates and more inpatient days in the first year after HCT.	Retrospective review of 325 (46 obese) allogeneic *adult* patients with hematologic malignancies treated before 2010 with multiple regimens. Obese (BMI > 30) (14%) were compared with normal (40%) or elevated BMI [25- ≤ 30] (46%). Median follow-up of 24 mo.	*Dosing*: Basis for dosing not reported but BSA was capped at 2.2 m^2 regardless of actual BSA. Variety of ablative and RIC regimens listed. Found allogeneic HCT acceptable choice. *Conclusion* Obese patients may be at increased risk for infection and require a higher level of care when undergoing allogeneic HCT.	[25]
Obese patients had a shorter overall survival.	Retrospective review 322 (242 *adult* and 80 *pediatric*, 91 obese) allogeneic patients with hematologic malignancies, aplastic anemia, or metabolic storage diseases, treated between 1983 and 1995 with an unreported chemotherapy regimen. Survival was 35% versus 20% ($P = .0045$) with a median of 262 d (nonobese) and 120 d (obese) follow-up.	*Dosing*: neither the conditioning regimen nor the basis for dosing was recorded. Relapse-related mortality was not significantly different between obese (17%) and nonobese (23%) ($P = .461$). The survival difference was significant in adults but not in a comparison of pediatric cases and controls. *Conclusion* Obese adults but not pediatric patients may have shorter nonrelapse-related survival with allogeneic HCT.	[26]
Toxicity varied by regimen but weight was predictive for mucositis (low or high weight) but not GVHD, sepsis, or SOS. No difference in TRM, PFS, or OS by weight.	Retrospective review of 262 (52 obese) *adult* patients (maximum 60 yrs old) with hematologic malignancies treated with multiple regimens before 2009. Only ablative regimens reviewed and actual body weights were adjusted per Metropolitan Life IBW tables for different frame sizes were used to test the use of large frame weight in place of TBW in obese individuals. Median follow-up of 11 to 23 mo, varying by regimen.	*Dosing*: If a patient's TBW was > than the top weight for their height, then the top weight in the large frame table was used. If TBW was < than the highest weight for their height, then TBW was used. BSA range, 1.28-2.4 m^2. *Conclusion* Obese patients may experience increased specific toxicities, but when viewed overall did not experience increased treatment-related or relapse-related mortality with allogeneic HCT.	[27]

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