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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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Table 1
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Outcomes	Basis	Comments	Reference
Obese allogeneic patients have a higher risk of NRM and inferior survival. Obese autologous patients have similar outcomes to nonobese.	Literature review – methods not reported.	*Dosing:* Recommend ABW25 for dosing weight going forward based upon current study reports. Adipose tissue may sequester lipophilic drugs. Need more consistent and biologically relevant definitions of obesity. IBW dosing may result in underexposure to some drugs. Review based primarily on myeloma/melphalan studies. Limited basis for other agents. *Conclusion* Obese allogeneic patients may have a higher risk for NRM while obese autologous patients do not appear to. This may be regimen related.	[4]
Alkylating agent–based reviews			
Obese patients had less mucositis and shorter LOS. No difference in relapse or survival was reported between groups.	Retrospective review of 80 (19 in highest dose/weight quartile) autologous adult patients with NHL treated between 2001 and 2005 with BEAM (melphalan dose used as surrogate marker). Median follow-up of 31.4 mo.	*Dosing*: Dosed upon BSA based on ABW25 if TBW > IBW. The actual patient weight versus their dose/weight quartile is not recorded or contrasted. *Conclusion* Obese patients may have less toxicity and similar survival with autologous HCT. May be regimen specific.	[28]
Patients with increased BMI had shorter time to engraftment and no difference in OS or LFS.	Retrospective review of 1662 *adults* (258 autologous, 1404 allogeneic, 77 obese) and 576 *pediatric* (79 autologous, 497 allogeneic, 13 obese) patients with hematologic malignancies or aplastic anemia treated between 1985 and 1992 with Bu(16) Cy(120) (TBW), Cy (200)ATG, CyTBI. Median follow-up of 150 d.	*Dosing*: majority dosed on TBW; however, cyclophosphamide, when dosed at 200 mg/kg over 4 d, was generally dosed at ABW50 based on physician preference. The number dosed in this manner is not recorded. *Conclusion* Obese adults and pediatrics can be safely treated with HCT deriving similar survival outcomes.	[29]
Obese patients have equivalent TRM and survival to those with normal weight patients and may have shorter time to engraftment.	Retrospective review of 192 MRD allogeneic *adults* (61 obese) with acute leukemia treated with multiple regimens between 2006-2009. Median follow-up of 15 mo.	*Dosing*: Chemotherapy was based on TBW and the primary regimen was Bu(16) Cy(120). RRT not reported, other than 1 death due to VOD. *Conclusion* Obese allogeneic HCT have similar survival to nonobese.	[30]
Obese patients had decreased mucositis, peak alkaline phosphatase, and no survival difference.	Retrospective review of 63 (13 obese) autologous *adults* treated before 2003 for AML with busulfan 16 mg/kg PO plus etoposide 60 mg/kg × 1. Median follow-up not reported.	*Dosing*: Dosed on ABW25. *Conclusion* Obese autologous patients may have less toxicity and equal survival. May be regimen specific.	[31]
The risk of death (reduced OS) of an overweight adult was 2.9 times that of a nonoverweight individual.	Retrospective review of 121 (28 obese) *adult* autologous NHL patients treated between 1990 and 1997 with either BEAM or high-dose mitoxantrone and melphalan. They were compared for outcomes with BMI < 28 compared with BMI ≥ 28.	*Dosing*: Dosed on TBW with a dose adjustment for 6 of 9 patients with a BMI ≥32. 77% had a BMI < 28 and 23% had a BMI ≥ 28 with 7 % overall ≥ 32. No significant difference was seen in RRT between groups with a nonsignificant decrease in the BMI ≥ 28 group. *Conclusion* Exercise caution in treating overweight NHL patients with autologous HCT as they may have lower survival.	[32]

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Table 1
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Outcomes	Basis	Comments	Reference
For melphalan based conditioning, obese patients had no difference in PFS, OS, disease progression, or NRM. However, for melphalan and TBI regimens obese and severely obese patients had better PFS, OS, and less progression but not better NRM.	Retrospective review of the CIBMTR database of 1087 autologous *adults* (109 obese, 125 severely obese) treated between 1995 and 2003 with melphalan or melphalan plus TBI for multiple myeloma. Median follow-up of 59 to 63 mo.	*Dosing*: Basis for dosing not reported. Analysis based on TBW from database showed reduced dosing of melphalan in 78% of severely obese, 56% of obese, 32% of overweight, and 11% of normal weight. There was no effect of dose reduction on PFS. *Conclusion* Obese autologous patients have similar survival, but this may be regimen dependent.	[12]
Obese allogeneic patients had similar outcomes when compared with nonobese patients with regard to mucositis, cardiotoxicity, emesis, and hyperglycemia. Nutritional status did not impact OS, PFS, or 100-day TRM.	Retrospective review of 71 *adult* allogeneic HCT patients (11 obese) with hematologic malignancies or MDS treated between 2003 and 2009 with Bu(12.8 or 16) Cy(120) or CyBu (numbers of each regimen not reported). Median follow-up not reported.	*Dosing*: Dosing was on TBW for normal and underweight (BMI $<$ 18.5) and based on ABW25 for overweight (BMI 25 to 29.9) and obese (BMI $\geq$ 30). *Conclusion* Obese allogeneic patients have similar levels of toxicity when dosed on adjusted body weight.	[33]
One and 2-year OS was worse in overweight children.	Retrospective review of CIBMTR database based on 1281 *pediatric patients* (143 overweight) with SAA treated with multiple cyclophosphamide-containing regimens with allogeneic HCT. Median follow-up $>$2 yrs.	*Dosing*: Dosing data not provided and no comment on the effect of dosing on outcomes. Other factors affecting survival were race, region, donor type, conditioning regimen in related donor HCT, performance score, and year of HCT. The impact of obesity on survival should be part of pretransplantation counseling for children with SAA. *Conclusion* Obese pediatrics undergoing allogeneic HCT for SAA may have decreased survival versus nonobese pediatrics.	[34]

ABW25 indicates IBW + .25(TBW-IBW); ABW40, IBW + .4(TBW-IBW); ABW50, IBW + .5(TBW-IBW); AML, acute myelogenous leukemia; ATG, antithymocyte globulin; BEAM, carmustine, etoposide, cytarabine, and melphalan; BMI, body mass index; BSA, body surface area; Bu, busulfan; Bu16, busulfan 16 mg/kg PO over 4 days; Bu12.8, busulfan 12.8 mg/kg i.v. at variable dosing frequencies; CIBMTR, Center for International Blood and Marrow Transplant Research; Cy, cyclophosphamide; Cy120, cyclophosphamide 120 mg/kg over 2 days; Cy200, cyclophosphamide 200 mg/kg over 4 days; GFR, glomerular filtration rate; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; IBW, ideal body weight; LFS, leukemia-free survival; LOS, length of stay; MRD, matched related donor; NHL, non-Hodgkin lymphoma; NRM, nonrelapse mortality; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; PO, oral; PTLD, post-transplantation lymphoproliferative disorder; RIC, reduced-intensity condition; RRT, regimen-related toxicity; SAA, severe aplastic anemia; SOS, sinusoidal obstruction syndrome; TBI, total body irradiation; TBW, total body weight; TRM, treatment-related mortality; URD, unrelated donor; VOD, veno-occlusive disease.

dose is further complicated because of wide variation in the dosing of chemotherapy used before HCT. There is variability based upon chemotherapy conditioning regimen agents, type of tumor treated, patient age, patient weight or size, and the therapeutic intent (myeloablative, reduced intensity without myeloablation, or autologous with stem cell rescue). With respect to patient weight, many attempts have been made to standardize dosing to achieve consistent therapeutic effects, while finding an acceptable or manageable level of toxicity in all patients. This has most frequently been attempted through the application of normalized formulas based upon body surface area, body weight, or pharmacokinetic- (PK) based formulas to accommodate for differences in body distribution, toxic effects, and metabolism between different chemotherapeutic agents. It is clear that there is no single dosing parameter for describing the PK of drugs in obese patients [6]. Other than for busulfan, the methods for dose adjustment to achieve targeted body exposures for specific agents within a preparative regimen are either poorly validated, not readily available, or both. Moreover, the target exposure required for optimal therapeutic outcomes can vary in different patient groups and remains a subject of discussion among transplantation professionals [7-9].

The 2012 panel review by the American Society of Clinical Oncology recommended that obese adult cancer patients, specifically excluding pediatrics, patients with hematologic malignancies, and those undergoing HCT, should be treated with full weight-based chemotherapy doses. This consensus was reached upon aggregate review of current data and there was no evidence for increased short- or long-term toxicity among obese patients who received full weight-based dose regimens [10]. However, a similar review has not been conducted among obese patients who underwent HCT, and previous studies have shown conflicting results in obese HCT recipients [11,12]. To address the need for evidence-based guidelines, the American Society for Blood and Marrow Transplantation Practice Guideline Committee conducted a comprehensive review of the literature to consider, if feasible, a position statement on conditioning chemotherapy dosing in obese HCT recipients. This report presents the Committee's recommendations for addressing this issue.

METHODS

A comprehensive review was performed of the PubMed and MEDLINE library databases between 1946 and June 2012 with hand searching of

Table 2
Dosing Recommendations for HCT 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^2 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. Pediatrics 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/C_{ss} 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^2 with multiple agent regimens. MTD of 1200 mg/m^2 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 pediatrics.	
Cytarabine	Dose adults and children on BSA based on TBW.	Cytarabine dosing generally lower than dose used in leukemia 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^2.
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 are 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^2, single-agent MTD is 900 mg/m^2 [36].
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 indicates IBW + .25(TBW-IBW); ABW40, IBW + .4(TBW-IBW); AUC, area under the curve; Bu, busulfan; BMI, body mass index; BSA, body surface area; C_{ss}, concentration at steady state; Cy, cyclophosphamide; Cy120, cyclophosphamide 120 mg/kg; Cy200, cyclophosphamide 200 mg/kg; DLT, dose-limiting toxicity; Flu, fludarabine; MTD, maximum tolerated dose; PK, pharmacokinetics; PO, oral; SOS, sinusoidal obstruction syndrome; TBW, total body weight; VOD, veno-occlusive disease.

selected reviews, meeting abstracts, and reference lists from selected and excluded articles. Articles published after the initial data search were monitored via Pubmed updates until September 2013. The literature search was limited to articles in English with human participants (Table 1). MESH headings and keywords searched were "stem cell transplantation," "obesity," "body size," and equivalent descriptors.

RESULTS

Based upon this review, the committee found they were unable to draw Level I or II evidence-based conclusions about how to dose HCT conditioning regimens in obese patients. This was due to the retrospective nature of reported studies; limited detail from case series; insufficient reporting of height, weight, and BMI; and variable use of PK-based targeting of chemotherapeutics. Although the literature primarily supports that obesity is not a barrier to good clinical HCT outcomes, the data are insufficient to determine optimal drug doses for conditioning obese individuals. This is complicated further in infancy and childhood by dramatic age-related differences in drug disposition and because known relationships between age and physiological processes might not still hold when obesity is also present [13,14].

Moreover, despite historic knowledge of maximum tolerated doses based on human tissue tolerability, current research reports provide evidence that known dose limits are not always taken into consideration. This is particularly apparent with the expanding number of nonablative conditioning protocols that report patient exposures to doses that meet or exceed those historically shown to cause harm [15].

Given the limitations of existing literature noted above and insufficient evidence to propose Level I or II recommendations, the committee decided instead to summarize current knowledge to support current practice and provide a basis for future research in this area. With this intent, we report the following consensus recommendations on conditioning therapy dosing as a basis to support the assessment and development of conditioning studies in obese patients (Table 2). Appendix 1 provides supporting data, which contains, when available, dosing information for obese patients, in addition to the general population. It also contains selected supporting or descriptive information to help medical providers assess the applicability of the dosing information to their respective patient populations.

It is important to note that the study of obese individuals has moved beyond the listing of actual versus ideal body weight, lean or fat-free weight, BMI, gender, and ethnicity-based weight indexes, and other measures based heavily upon a variety of mathematical models [1]. In an effort to discern the larger but healthy, or "fit" individual, there are now models which use radiographic techniques, bioelectric impedance, fat distribution assessment, and other methods that may be technically more accurate in assessing an individual's body composition but are of undocumented applicability when it comes to the dosing of individual drugs [1]. Given the current limited reporting of patient physical demographics (frequently just age and gender), these newer and possibly more accurate methods of weight assessment are not yet validated for use with medication dosing and, thus, not applicable for daily use.

The recommendations for dosing chemotherapeutic agents in HCT conditioning regimens are described in Table 2 and are based on the articles listed in Table 1 and Appendix 1. The following standardized definitions were used: overweight: BMI 25 to < 30 kg/m^2; obese: BMI ≥ 30 to 34 kg/m^2; morbidly obese: BMI 35 to 39 kg/m^2; and extremely obese: BMI ≥ 40 kg/m^2. It should also be noted that, although pediatric data are more limited than adult data, they have been provided when adequate supporting information was available.

CONCLUSIONS

Review of the literature provides the following tenets when dosing antineoplastics for disease control and prevention of graft rejection in the setting of autologous and allogeneic HCT:

- In both the ablative and nonablative settings, some drug doses have been titrated beyond myelosuppression to the next dose-limiting toxicity. For example, cyclophosphamide is dosed at 4 to 8 times the doses seen in conventional antineoplastic therapy, such that cardiac toxicity becomes the dose-limiting factor [16].
- The dose-limiting toxicity of each agent within a conditioning regimen may vary, depending on 1 or more other agents with which it is combined. For example, carmustine toxicity occurs at a significantly different dose in combination versus as a single agent [17,18].
- Obese patients often have comorbidities that further affect drug disposition or tolerance.
- Supportive care advances and current PK practices have allowed further dose advancement and have diminished the occurrence of some previously common toxicities associated with HCT for some medications, primarily busulfan [19-22].
- To help advance the field, we suggest that journals mandate that future research publications on this topic and those that describe conditioning regimens incorporate the critical parameters of height, weight, body surface area, and BMI to provide more meaningful clinical outcomes assessments.

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Appendix 1
Evidence for Chemotherapy Dose Adjustment

Agent	Dosing Basis	Patient Population	Comments	Reference
Alemtuzumab	Same dose regardless of BSA (20 mg d × 5 d).	Phase I/II study of clofarabine, melphalan, and alemtuzumab in 82 allo *adult* patients with mixed hematologic malignancies, MPD, or MDS. Treatment period before 2012 but was not reported specifically. Median follow-up was 25 mo.	Body weight parameters not provided. RRT-related mortality of 19% in first 100 d. Multiple cases of renal toxicity, sepsis (4), cardiac deaths (3 with 1 in an obese patients), and 1 irreversible encephalopathy. No SOS/VOD.	[37]
Busulfan	Dosed on TBW.	Retrospective review of 1662 *adults* (258 auto, 1404 allo) and 576 *pediatrics* (79 auto, 497 allo) patients with hematologic malignancies or aplastic anemia treated between 1985 and 1992 with Bu(16) Cy(120 or 200), CYATG, or CYTBI (TBW) at a single institution. Distribution was <95% IBW (187), 95%-145% IBW (1398), and >145% IBW (77). Median follow-up of 150 d.	Patients >145% versus 95% to 145% had shorter time to engraftment and no difference in OS or DFS. Those with <85% IBW did worse. 77 obese adults and 13 obese children in sample.	[29]
Busulfan	Dosed on TBW.	Retrospective review of 192 allo *adults* (61 obese) with acute leukemias treated with multiple regimens between 2006 and 2009. Patients conditioned with Bu (16) Cy(120) (on TBW) for MRD HCT. Median age 28 (15-57). Median follow-up of 15 mo.	Increased BMI had shorter time to engraftment and no difference in OS or LFS. No significant difference in 1-yr TRM between normal weight and obese patients. Overweight/obese defined as BMI >25. No information on level of obesity. RRT not reported, other than 1 death due to VOD.	[30]
Busulfan	Dosed on ABW25.	Retrospective review of 63 auto *adults* treated before 2003 (actual time period not reported) for AML with Bu 1 mg/kg/dose PO for 16 doses plus E 60 mg/kg for 1 dose. Median follow-up not reported.	Observed decreased mucositis and peak alkaline phosphatase in the obese patients with no survival difference. Small patient groups, 13 patients ≥ 130% IBW were compared with 19 patients at 97%-103% IBW.	[31]
Busulfan	Dosed based on the lesser of TBW or IBW. -Based on institutional practice and ABW (adjustment not stated) could be used.	61 *adult* allo patients with mixed hematologic malignancies or MDS treated between 1996 and 1997 conditioned with Bu .8 mg/kg/dose i.v. every 6 h for 16 doses without targeting PK and Cy 60 mg/kg for 2 doses. Median follow-up 28 mo.	Patient weight parameters not provided. 5 cases SOS (8.2%, 2 fatal), 44% grade 2, and 26% grade 3 mucositis, 1 interstitial pneumonitis, 2 pneumonia with DAH.	[38]
Busulfan	Dosed on TBW up to 120% of IBW then dosed on ABW50.	36 *adult* allo patients with CML treated between 1996 and 2001 with BuCy2. Bu 16 mg/kg PO over 4 d targeted to 1250 μmol/min ± 20% and Cy 60 mg/kg for 2 d. Median follow-up not reported.	Stated AUC target of 950-1520 μmol/min is optimal for BuCy2. No VOD, 47% grade 2/3 mucositis, 17% grade 3 diarrhea. Weight parameters for patients not reported.	[39]
Busulfan	Dosed on TBW and used test dose for PK targeting for obese and nonobese.	Retrospective chart review of 68 *pediatric* allo HCTs with a mixture of malignant and nonmalignant disorders treated between 2003 and 2008. BuFluATG(r) or BuFluECP dosed on TBW with single daily i.v. Bu dose given based upon the Bu test dose PK to target 4000 to 5000 ± 800 μmol/min. Bu test dose of .8 mg/kg infused over 3 h 5-7 d before HCT conditioning, targeting an AUC of 1000 micromole/min. Median follow-up not reported.	Dosing needs to be PK based for *pediatrics*. 32% of the children were obese as defined by >85th percentile of age adjusted BMI. The lowest dose/kg and lowest Bu clearance were observed in obese, thus requiring lower Bu doses. RIC regimens used with no toxicity data provided.	[40]

Busulfan	Dosed on the lesser of IBW or TBW unless >120% IBW then ABW25 at FIRST site and all patients received Bu and Cy doses based on ABW25 at a SECOND treatment site.	382 *adults* with NHL treated between 1992 and 1998 with auto HCT conditioned with Bu 1 mg/kg/dose PO for 14 doses, E 60 mg/kg for 1 dose, and Cy 60 mg/kg/d for 2 doses. Median follow-up 33 mo.	2.9% SOS/VOD. Stated that use of ABW minimized differences in clearance between obese and nonobese. Called for studies to start reporting body size units to allow meaningful comparison of patient data. 26 obese patients and 248 that met ABW dosing criteria.	[41]
Busulfan	Dosed patients at .44- 1.8 mg/kg TBW PO every 6 h for 4 d with PK on the 5th and 9th doses.	279 *adolescent* and *adult* (ages 13 to 60) allo and auto (breakdown not reported) patients treated at a single center between 1992 and 1996 for hematologic malignancies, breast cancer, ovarian cancer, or MDS with PK-targeted Bu PO Q 6 h × 4 d (16 doses). Compared underweight, normal, obese, and severely obese patients for HCT for a variety of cancers. Additional agents or TBI could be given after Bu but not before it. Median follow-up not reported.	No patients <12 yrs old. Grade III/IV RRT seen related to high Bu exposure. Graft rejection related to low Bu exposure. Recommended dosing adult patients on ABW25 to remove variability based on body size; however, dosing based on AUC or Css is required to compensate for other metabolic and genetic variables. Weight categories defined as underweight (BMI < 18 [n = 7], normal (BMI 18-26.9 [n = 173]), obese (BMI 27-35 [n = 89]), severely obese (BMI > 35 [n = 10]).	[42]
Busulfan	Dosed on BSA, based on TBW, some patients dosed with PK targeting	102 *adult* autoHCT patients with advanced lymphoid malignancies treated between 2005 and 2008 with Bu 130 mg/m^2 i.v. for 4 d or to target 5000 ± 12% μmol/min d and melphalan 70 mg/m^2 for 2 d. Median follow-up of 34 mo.	1 case SOS and no grade IV toxicities. No patient weight parameters reported.	[43]
Busulfan	Dosed on TBW and adjusted to meet target AUC based on phase I study criteria starting at a daily AUC of 4800 μmol/min.	Phase 1 trial of 36 *adult* allo HCT treated between 2005 and 2007 for a variety of hematologic malignancies. Conditioning regimen contained Bu at either 3.2 mg/kg i.v. or adjusted dose daily based on a .5 mg/kg test dose within 8 d of starting plus fludarabine 25 mg/m^2/d and alemtuzumab 20 mg/d × 5 d.	MTD of 5800 μmol/min/L with DLT of 62.5% SOS/VOD at AUC of 6800 μmol/min/L. No patient weight parameters reported. SOS may be associated with peak busulfan level.	[7]
Busulfan	Dosed on TBW calculated BSA with PK targeting.	Phase I trial of 72 *adult* MMUD allo HCT treated between 2005 and 2010. Bu targeted daily AUC levels: group 1 (6000 ± 600), group 2 (7500 ± 750), or group 3 (9000 ± 900) μmol/min with initial dose of 170 mg/m^2, 180 mg/m^2, or 220 mg/m^2/daily i.v. respectively for 4 d. Patients also received Flu 40 mg/m^2/d for 4 d, and ATG(r) 3.25 mg/kg/d for 2 d. Minimum follow-up of 10 mo.	No patient weight parameters provided. SOS/VOD was the DLT with 0 at level 1, 7% at level 2, and 100% at level 3. No difference in NRM between levels 1 and 2.	[8]
Busulfan	Dosed on IBW with PK targeting in a subgroup of 12 patients.	70 *adult* allo patients with a variety of hematologic disease states and MDS treated between 1999 and 2001. Conditioned with Bu 3.2 mg/kg i.v. for 4 d plus Flu 50 mg/m^2 for 5 d plus ATG(r) 4.5 mg/kg over 3 d. Median follow-up 16 mo.	1 Bu-related seizure, 70% grade II stomatitis, 74% ALT increases with 1 SOS, no reporting of cognitive/neurotoxic effects of fludarabine. Mean daily Bu AUC of 4900-5000 μmol/min. No patient weight parameters reported.	[44]
Busulfan	Dosed on IBW.	50 *adult* (16-50 yrs old) allo patients with varied leukemias treated between 1984 and 1986. Conditioned with Bu 1 mg/kg PO for 16 doses plus Cy 60 mg/kg for 2 doses. Follow-up 6 to 36 mo with no median reported.	1 case of SOS, 5 cases severe hemorrhagic cystitis. Most symptoms reported descriptively and not graded. No patient weight parameters reported.	[45]

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Appendix 1
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Agent	Dosing Basis	Patient Population	Comments	Reference
Busulfan	Dosed on ABW25 if > 130% IBW and lesser of TBW or IBW if ≤ 130% IBW.	Retrospective review of 294 *adult* auto patients treated between 1999 and 2010 with BuCyE for lymphoma compared PK-guided results of oral Bu versus 2 i.v. Bu schedules. BMI's ranged as high as 62 and BMI was not associated as a change in OS. 16 mg/kg PO or 12.8 mg/kg i.v. targeted to AUC 20,000 (18,400-21,600) μmol/min off first dose PK. Median follow-up varied by group from 311 to 1565 d.	100-d RRT 2.1%-3.5% across groups and causes of death not listed. BMI range and average shown but not percent of obese patients and no obese subset analysis. PK-guided Bu is equivalent in outcomes whether PO-16 doses, i.v.-16 doses, or i.v.-4 doses if guided to the same exposure target.	[46]
Busulfan	Dosed on ABW25.	Retrospective literature review of multiple public databases with unclear search parameters. Single obese *adult* allo HCT CML patient treated with Bu(12.8) Flu(150) ATG(e)(60) versus 9 normal-weight patients treated at the same institution. Dates of patient therapy not reported. Duration of follow-up unreported.	Busulfan AUC target (900-1500 μmol/min) from first dose PK sampling showed similar plasma concentrations compared with normal-weight patients on the same regimen.	[47]
Busulfan	Dosed on TBW.	Retrospective review of 48 *pediatric* allo and auto patients with malignant and nonmalignant disorders treated between 1997 and 2001 with oral Bu(16) plus 1-2 additional agents. Duration of follow-up not reported.	Patients were 0.4-18 years old and BSA of 0.29-2 m^2. Individual patient parameters not correlated with patient weight. Best correlation was between PK parameters and dosing on TBW.	[48]
Busulfan	Dosed on ABW25 for per kilogram dosing or actual TBW-based BSA if BSA-based.	Retrospective population PK model created from 5 studies of 127 *adult* patients with mixed hematologic malignancies and MDS treated between 1996 and 1997 treated with Bu(12.8 mg/kg) Cy(120). Model contains 6 underweight, 71 normal- weight, 39 obese, and 11 severely obese people. Follow-up not recorded.	I.V. busulfan has the most consistent PK with target levels when dosed on ABW25 for per kilogram dosing and BSA based on TBW. Limited sampling strategies are effective for adjusting busulfan dosing to achieve target drug levels.	[49]
Busulfan	Dosed on TBW.	Prospective evaluation of 24 *pediatric* patients with malignant hematologic or nonmalignant disorders conditioned before 2007 for allo HCT with Bu(12.8 or 16) Cy(200). Busulfan was dosed to achieve target AUC of 950-1350 μmol/min. Duration of follow-up not reported.	Busulfan was dosed i.v. at 1 mg/kg ≤ 4 yrs old and .8 mg/kg >4 years old, then adjusted to target AUC (1 patient not adjusted). No weight parameters for patients were reported, unclear if sample contained obese patients. 21% VOD observed. Suggested dosing based on PK model created is 1.1 mg/kg for ≤ 12 kg and .8 mg/kg for >12 kg patients.	[50]
Carboplatin	Dosed on BSA based on the lesser of IBW or TBW.	Retrospective review of 117 *adults* and *children* with a variety of solid tumors (mainly breast tumors in adults) treated with and auto HCT between 1994 and 1999. Conditioned with Cy 2000 mg/m^2 plus carboplatin 600 mg/m^2 daily for 3 d. Median follow-up not reported.	AUC was calculated retrospectively for each individual using the Calvert formula. Daily AUC >7 was associated with higher levels of ≥ grade 2 nonhematologic toxicity. Weight parameters not reported. Number of pediatric patients not reported.	[51]
Carboplatin	Dosed patient on TBW.	Single *adult* auto breast cancer patient (BMI 47) case report treated before 2002 (date not reported) with Cy 1000 mg/m^2/d plus thiotepa 80 mg/m^2/d plus carboplatin AUC 3.25/d for 4 d. PK drug values were compared with normal population using PK targeting. Duration of follow-up not reported.	No specific toxicity or clinical data provided. Suggested dosing in obese was carboplatin AUC based on ABW 50. Comparator population data derived from both HCT and non-HCT population data.	[52]

Carboplatin	Dosed on BSA based on TBW.	46 *adults* with a variety of solid tumors treated before 2001 (actual dates not reported) with single or multiple courses of either Cy 1500 mg/m^2 plus carboplatin 400 mg/m^2 plus thiotepa 120 mg/m^2 daily for 4 d or the same agents at two-thirds the dose. Median follow-up not reported.	Relationships were identified between elevated transaminases and thiotepa and TEPA AUC, mucositis, and TEPA AUC, ototoxicity and carboplatin AUC, and a trend towards 4-hydroxycyclophosphamide AUC and VOD. No patient weight parameters reported.	[53]
Carmustine	Dosed on BSA based on TBW. If TBW > IBW, then dosed on BSA based on ABW25.	Retrospective review of 80 (19 in highest dose/weight quartile) *adult* auto patients with NHL treated between 2001 and 2005 with BEAM (melphalan dose used as surrogate marker). Median follow-up of 31.4 mo. Care performed primarily as an outpatient.	BSA-based melphalan doses >3.6 mg/kg based on TBW significantly increased rates of grade III/i.v. mucositis and increased lengths of hospital stay were seen. Dose correlation with BMI or body habitus not performed with quartile placement. Obese patients had less mucositis and shorter LOS, and no difference in relapse or survival.	[28]
Carmustine	Dosed on BSA based on TBW up to 120% IBW, then ABW50.	85 *adult* female auto patients being treated before 2001 (actual dates not reported) for breast cancer treated with Cy 1875 mg/m^2/d for 3 d plus cisplatin 165 mg/m^2 over 3 d plus carmustine 600 mg/m^2 for 1 d. 25 patients were >120% IBW. Median follow-up not reported.	Obese patients had significantly lower cisplatin concentrations and lower, but not significantly, Cy concentrations with similar carmustine concentrations. Carmustine concentrations in those with pulmonary toxicity were not different than those who did not. No patients were morbidly obese, >2 times IBW.	[54]
Carmustine	Dosed on BSA based on TBW.	29 *adults* with varied solid tumors treated before 1986 (actual dates not reported) on a phase I auto study of escalating doses of Cy, cisplatin, and carmustine. No median follow-up reported.	MTD of carmustine when dosed with cyclophosphamide and cisplatin is 600 mg/m^2. DLT is VOD/SOS for the combination. Patient weight parameters not reported.	[17]
Carmustine	Dosed on BSA based on TBW.	143 *adult* and *pediatric* patients with refractory solid and hematologic cancers treated between 1978 and 1980 with escalating doses of carmustine with auto marrow rescue. Median follow-up not reported, 4 patients remained alive when article written.	MTD of 1200 mg/m^2 due to lung and liver toxicity. 9.5% pulmonary toxicity. No patient weight parameters reported. Number of pediatric patients not reported.	[18]
Carmustine	Dosed on BSA based on TBW.	35 *adults* with a variety of solid tumors treated between 1978 and 1980 with escalating dose carmustine with auto marrow rescue in a phase I trial. No median follow-up reported.	Visceral toxicities (hepatic and pulmonary) are dose limiting above 600 mg/m^2. No patient weight parameters reported.	[55]
Clofarabine	Dosed on BSA based on TBW. 40 mg/m^2/d for 5 d.	Phase I/II study of clofarabine, melphalan, and alemtuzumab in 82 allo *adult* patients with mixed hematologic malignancies, MPD, or MDS. Treatment period was before 2012 but was not reported specifically. Median follow-up was 25 mo.	Body weight parameters not provided. RRT-related mortality of 19% in first 100 d. Multiple cases of renal toxicity, sepsis (4), cardiac deaths (3 with 1 in an obese patient), and 1 irreversible encephalopathy. No SOS/VOD.	[37]
Cyclophosphamide	Dosed on TBW except Cy 200 mg/kg, which was generally dosed on ABW50 based on physician preference. The number dosed in this manner is not recorded.	Retrospective review of 1662 *adults* (258 auto, 1404 allo) and 576 *pediatric* (79 auto, 497 allo) patients with hematologic malignancies or aplastic anemia treated between 1985 and 1992 with Bu(16) Cy(120 or 200), CYATG, or CYTBI (TBW) at a single institution. Distributed as < 95% IBW (187), 95%-145% IBW (1398), and > 145% IBW (77). Median follow-up 150 d.	Patients > 145% versus 95%-145% had shorter time to engraftment and no difference in OS or DFS. <85% IBW did worse. 77 obese adults and 13 obese children in sample.	[29]

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Appendix 1
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Agent	Dosing Basis	Patient Population	Comments	Reference
Cyclophosphamide	Dosed on TBW.	Retrospective review of 192 allo *adults* (61 obese) with acute leukemias treated with multiple regimens between 2006 and 2009. Patients conditioned with Bu (16) Cy(120) for MRD HCT. Median age 28 (15-57). Median follow-up of 15 mo.	Increased BMI had shorter time to engraftment and no difference in OS or LFS. No significant difference in 1 year TRM between normal weight and obese patients. Overweight/obese defined as BMI >25. No information on level of obesity. RRT not reported, other than 1 death due to VOD.	[30]
Cyclophosphamide	Dosed based on the lesser of TBW or IBW.	61 *adult* allo patients with mixed hematologic malignancies or MDS treated between 1996 and 1997 conditioned with Bu .8 mg/kg/dose i.v. every 6 h for 16 doses without targeting PK and Cy 60 mg/kg/d for 2 doses. Median follow-up 28 mo.	Patient weight parameters not provided. 5 cases SOS (8.2%, 2 fatal), 44% grade 2, and 26% grade 3 mucositis, 1 interstitial pneumonitis, 2 pneumonia with DAH.	[38]
Cyclophosphamide	Dosed on the lesser of TBW or IBW.	36 *adult* allo patients with CML treated between 1996-2001 with BuCy. Bu 16 mg/kg PO over 4 d targeted to 1250 μmol/min ± 20% and Cy 60 mg/kg/d for 2 d. Median follow-up not reported.	Stated AUC target of 950-1520 μmol/min is optimal for BuCy2. No VOD, 47% grade 2/3 mucositis, 17% grade 3 diarrhea. Weight parameters for patients not reported.	[39]
Cyclophosphamide	Dosed on the lesser of IBW or TBW unless >120% IBW, then ABW25 at FIRST site and all patients received Bu and Cy doses based on ABW25 at a SECOND treatment site.	382 *adults* with NHL treated between 1992 and 1998 with auto HCT conditioned with Busulfan 1 mg/kg/dose PO for 14 doses, E 60 mg/kg for 1 dose, and Cy 60 mg/kg/d for 2 doses. Median follow-up 33 mo.	2.9% SOS/VOD. Stated that use of ABW minimized differences in clearance between obese and nonobese. Called for studies to start reporting body size units to allow meaningful comparison of patient data. 26 obese patients and 248 that met ABW dosing criteria.	[41]
Cyclophosphamide	Dosed on IBW.	50 *adult* (16-50 yr old) allo patients with leukemias treated between 1984 and 1986. Conditioned with Bu 1 mg/kg/dose PO for 16 doses plus Cy 60 mg/kg/dose for 2 doses. Follow-up 6 to 36 mo with no median reported.	1 case of SOS, 5 cases severe hemorrhagic cystitis. Most symptoms reported descriptively and not graded. No patient weight parameters reported.	[45]
Cyclophosphamide	Dosed on TBW if ≤ 130% IBW and ABW50 if >130% IBW.	Retrospective review of 294 *adult* auto patients treated between 1999 and 2010 with BuCyE for lymphoma compared PK-guided results of oral Bu versus 2 i.v. Bu schedules. BMI's ranged as high as 62 and BMI was not associated with changes in OS. 16 mg/kg PO or 12.8 mg/kg i.v. targeted to AUC 20,000 (18,400-21,600) μmol/min/d with first dose PK. Dosed Cy at 60 mg/kg/d on d -3 and -2. Median follow-up varied by group from 311 to 1565 d.	100-d RRT 2.1%-3.5% across groups and cause of death not listed. BMI range and average shown but not percent of obese patients and no obese subset analysis. PK guided Bu is equivalent in outcomes whether PO-16 doses, i.v.-16 doses, or i.v.-4 doses if guided to the same exposure target.	[46]
Cyclophosphamide	Dosed on TBW.	Single *adult* auto breast cancer patient (BMI 47) case report treated before 2002 (date not reported) with Cy 1000 mg/m^2/d plus thiotepa 80 mg/m^2/d plus carboplatin AUC 3.25/d for 4 d. PK drug values compared with normal population using PK targeting. Duration of follow-up not reported.	No specific toxicity or clinical data provided. Suggested dosing in obese with Cy on ABW40-based BSA. Population data derived from HCT and non-HCT population data.	[52]

Cyclophosphamide	Dosed with BSA based on TBW up to 120% IBW then ABW50.	85 *adult* female auto patients being treated before 2001 (actual dates not reported) for breast cancer treated with Cy 1875 mg/m^2/d for 3 d plus cisplatin 165 mg/m^2 over 3 d plus carmustine 600 mg/m^2 for 1 d. 25 patients were >120% IBW. Median follow-up not reported.	Obese patients had significantly lower cisplatin concentrations and lower, but not significantly so, Cy concentrations with similar carmustine concentrations. Carmustine concentrations in those with pulmonary toxicity were not different than those who did not. No patients were morbidly obese, defined as >2 times IBW.	[54]
Cyclophosphamide	Dosed on BSA based on TBW.	29 *adults* with solid tumors treated before 1986 (actual dates not reported) on a phase I auto study of escalating doses of Cy, cisplatin, and carmustine. No median follow-up reported.	MTD of carmustine when dosed with Cy and cisplatin is 600 mg/m^2. DLT is VOD/SOS for the combination. Patient weight parameters not reported.	[17]
Cyclophosphamide	Dosed on TBW.	80 *adults* and *pediatrics* treated between 1972 and 1985 with allo HCT for nonmalignant conditions. Conditioned with Cy200 mg/kg or Bu(16) Cy(200) + ATG. Median follow-up not reported.	17% cardiotoxicity within 10 d of Cy infusion, 43% fatal. DLT for 4-d regimen with or without Bu. Primarily an adult issue and suggested not to exceed 1.55 g/m^2 in adults. Weight parameters for patients not reported.	[16]
Cyclophosphamide	Dosed on TBW.	196 *adult* and *pediatric* (9 < 20 years old) patients with CML treated between 1985 and 1994 with an allo HCT conditioned with TBI 1350 plus Cy 120 mg/kg over 2 d. Median follow-up of 5 yr.	No RRT reported or TRM due to organ failure reported. Increased body weight index increased risk of death 1.6 times. 14% >125% IBW and 9% >140% IBW. Unclear if the obese patients were adult or pediatric.	[56]
Cyclophosphamide	Dosed on TBW.	Retrospective review of 54 (9 obese) *adult* patients with AML treated between 1981 and 1999 with an auto HCT. Conditioned with Bu (16 mg/kg over 4 d) Cy 120 mg/kg over 2 d. Median follow-up 76.5 mo.	TRM obese 33% (n = 3) and 8% (n = 3) nonobese. Specific toxicities not provided. Overall survival at median 76.5 mo of 0.22 obese versus 0.63 nonobese (P = .012).	[57]
Cyclophosphamide	Dosed on TBW.	12 *adult* patients with solid tumors treated before 1975 (actual dates not reported) without auto rescue given Cy 60 mg/kg/d × 2 d. Median follow-up not reported.	33% cardiac toxicity; none fatal. No weight parameters reported.	[58]
Cyclophosphamide	Dosed on TBW.	Retrospective review of 61 *adult* and *pediatric* patients with SAA treated between 2006 and 2011 with an allo URD HCT on the BMTCTN 0301 clinical trial. Conditioned with Cy at the 150 mg/kg, 100 mg/kg, 50 mg/kg, or 0 mg/kg dosing levels in addition to ATG(r) 3 mg/kg/d or ATG (e) 30 mg/kg/d for 3 d plus fludarabine 30 mg/m^2/d for 4 d, and TBI 200 cGy for 1. Median follow-up not reported.	Phase I/II trial resulted in 7 of 14 patient deaths at the 150-mg/kg dose. 2 of pulmonary failure, 2 of ARDS, 1 multiorgan failure, 1 cardiac failure, and 1 viral infection. Ages 9-61 (2 children and 5 adults). Weight parameters not shown.	[59]
Cyclophosphamide	Dosed on ABW25.	Retrospective review of 72 *adults* with CML treated with Cy120TBI allo HCT between 1992 and 1999. Median follow-up duration unclear, followed through d +18 for mucositis.	Weights up to 132 kg and BMI up to 42.7 treated but number of obese patients not reported. BMI >25 was associated with increased risk for oral mucositis.	[60]
Cytarabine and etoposide in BEAM regimen	Dosed on BSA based on ABW25.	Retrospective review of 80 (19 in highest dose/weight quartile) auto *adult* patients with NHL treated between 2001 and 2005 with BEAM (melphalan dose used as surrogate marker). Median follow-up of 31.4 mo. Care performed primarily as an outpatient.	At BSA-based melphalan doses >3.6 mg/kg based on TBW significantly increased rates of grade III/IV mucositis and increased lengths of hospital stay were seen. Dose correlation with BMI or body habitus not performed with quartile placement. Obese patients had less mucositis and shorter LOS, and no difference in relapse or survival.	[28]

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Agent	Dosing Basis	Patient Population	Comments	Reference
Etoposide	Dosed adult patients on ABW25 for E.	Retrospective review of 63 auto *adults* treated before 2003 (actual time period not reported) for AML with Bu16 plus E 60 mg/kg for 1 dose. Median follow-up not reported.	Observed decreased mucositis, peak alkaline phosphatase in the obese patients with no survival difference. Small patient groups, 13 patients $\geq$ 130% IBW were compared with 19 patients at 97%-103% IBW.	[31]
Etoposide	Dosed adult patients on TBW if $\leq$ 130% IBW and ABW50 if >130% IBW.	Retrospective review of 294 *adult* auto patients treated between 1999 and 2010 with BuCyE for lymphoma compared PK-guided results of oral Bu versus 2 i.v. Bu schedules. BMI's ranged as high as 62 and BMI was not associated with changes in OS. 16 mg/kg PO or 12.8 mg/kg i.v. targeted to AUC 20,000 (18,400-21,600) μmol/min off first dose PK. Dosed etoposide at 10 mg/kg on d −4, −3, and −2. Median follow-up varied by group from 311 to 1565 d.	100-d RRT 2.1-3.5% across groups and cause of death not listed. BMI range and average shown but not percent of obese patients and no obese subset analysis. PK-guided Bu is equivalent in outcomes whether PO-16 doses, i.v.-16 doses, or i.v.-4 doses if guided to the same exposure target.	[46]
Etoposide	Dosed on TBW.	90 *adult* and *pediatric* AML patients (28 auto, 62 allo) treated between 1991 and 1998 conditioned with Bu16 plus Cy (30 mg/kg/dose for 2 doses) plus E 30 mg/kg/dose versus 45 mg/kg/dose for 1 dose. Median follow-up of 16 mo.	30 mg/kg preferred due to higher liver toxicity and SOS, mucositis, infections, interstitial pneumonitis, and overall TRM in the 45-mg/kg arm. Number of pediatric patients not reported. Patient weight parameters not reported.	[61]
Fludarabine	Dosed on BSA calculated from TBW.	70 *adult* allo patients with hematologic malignancies or MDS treated between 1999 and 2001. Conditioned with Bu 3.2 mg/kg/d i.v. for 4 d plus Flu 50 mg/m^2 × 5 d, ATG(r) 4.5 mg/kg over 3 d. Median follow-up 16 mo.	1 Bu-related seizure, 70% grade II stomatitis, 74% ALT increases with 1 SOS, no reporting of cognitive/neurotoxic effects of fludarabine. Mean daily Bu AUC of 4900-5000 μmol/min. -No patient weight parameters reported.	[44]
Fludarabine	Dosed on BSA based on TBW.	Retrospective review of 61 *adult* and *pediatric* patients with SAA treated between 2006 and 2011 with an allo URD HCT on CTN 0301 clinical trial. Conditioned with Cy at the 150 mg/kg, 100 mg/kg, 50 mg/kg, or 0 mg/kg dosing levels plus ATG(r) 3 mg/kg/d or ATG(e) 30 mg/kg/d for 3 d plus fludarabine 30 mg/m^2/d for 4 d, and TBI 200 cGy for 1 dose. Median follow-up not reported.	Phase I/II trial resulted in 7 of 14 patient deaths at the 150-mg/kg dose. 2 of pulmonary failure, 2 of ARDS, 1 multiorgan failure, 1 cardiac failure, and 1 viral infection. Ages 9-61 (2 children and 5 adults). Weight parameters not shown.	[59]
Melphalan	Dosed with BSA based on TBW. If TBW > IBW then dosed on BSA based on ABW25.	Retrospective review of 80 (19 in highest dose/weight quartile) *adult* auto patients with NHL treated between 2001 and 2005 with BEAM (melphalan dose used as surrogate marker). Median follow-up of 31.4 mo. Care performed primarily as an outpatient.	At BSA-based melphalan doses > 3.6 mg/kg based on TBW significantly increased rates of grade III/IV mucositis and increased lengths of hospital stay were seen. Dose correlation with BMI or body habitus not performed with quartile placement. Obese patients had less mucositis and shorter LOS, and no difference in relapse or survival.	[28]
Melphalan	Dose on BSA based on TBW or other weight per institutional practice.	197 *adult* auto HCT patients treated before 2008 (actual dates not reported) with myeloma (n = 109) or NHL (n = 88) conditioned with either melphalan 200 mg/m^2 or BEAM chemotherapy respectively. Patients weighing up to 135 kg were treated but prevalence of obese patients was not reported.	Oral mucositis prospectively reviewed daily until 30 d after transplantation. Severe oral mucositis occurred in 46% with myeloma and 42% with NHL. Severe oral mucositis decreased as BSA increased resulting in a lower mg/kg melphalan dose. <4.75 mg and > 5.25 mg/kg had less and more significant mucositis respectively.	[62]
Melphalan	Dosed on BSA based on IBW.	716 *adult* patients with myeloma treated between 2000 and 2007 with auto HCT. Conditioned with single-agent melphalan 200 mg/m^2 for 1 dose.	100-d mortality declined over time to <1% in last 2 yr. Patient weights not reported. RRT not reported.	[63]

Melphalan	BSA based on TBW if $\leq$ 60 kg. BSA based in ABW40 if >60 kg.	381 *adult* patients with myeloma treated between 1998 and 2002 with auto HCT. Conditioned with single-agent melphalan 200 mg/m^2 (n = 350) or 140 mg/m^2 (n = 31) for 1 dose. Patient follow-up 60 d for mucositis. OS not evaluated.	Dose decreased to 140 mg/m^2 if serum creatinine >3. Recommended dose not be adjusted in obese based on mucositis end points. 3.4 mg/kg was the break point where increased rates of grade III/IV mucositis were seen when it was exceeded. BMI range 17.4-55 (median 26.6), mg/kg weight and mucositis decreased as BMI increased. Maximum weight 160 kg but number of obese patients not reported.	[64]
Melphalan	Dosed on BSA based on TBW or if obese BSA based on (IBW + 15 kg + ABW40).	89 consecutive outpatient *adult* myeloma patients treated with auto HCT between 2001 and 2004 at a cycle dose of 140 (>65 yr old or decreased performance status, n = 14) or 200 mg/m^2 (n = 75). Both doses given over 2 d. Median duration of follow-up not reported.	Obesity not defined. Number of obese patients not listed. No RRT-related deaths.	[65]
Melphalan	Dosed on BSA based on TBW.	33 *adult* (26) and *pediatric* (7) patients with varied solid tumors treated between 1980 and 1982 with escalating doses of melphalan with auto at 120-225 mg/m^2/cycle. Median follow-up not reported.	Single-agent DLT (stomatitis, esophagitis, and diarrhea) at 225 mg/m^2. Suggested 180 mg/m^2 over 3 d as the MTD. No patient weight information provided.	[66]
Melphalan	BSA based on TBW.	Prospective review of 52 *children* receiving HCT (allo or auto not reported) for malignancies before 2004. Melphalan was dosed in 1 of 12 different regimens with or without other agents. Melphalan PK were performed, some with a test dose. Duration of follow-up not reported.	Melphalan PK varied with concomitant agents, carboplatin increased AUC and decreased clearance. Melphalan PK varied and was triphasic (n = 36) or biphasic (n = 16) depending on the individual. Weight explained up to 80%-85% of the variability in children's PK based on PK parameter. No patient specific weight parameters were reported.	[67]
Thiotepa	Dosed on BSA based on IBW.	15 *adult* patients (8 allo and 7 auto) with hematologic malignancies treated before 1995 (actual dates not reported) with Bu 1 mg/kg/dose PO for 10 doses, Cy 60 mg/kg/dose for 2 or 3 d, and 250 mg/m^2/dose for 3 d. Median follow-up not reported.	Maximum RRT worse for patients at IBW than for obese patients dosed on IBW but similar RRT for obese patients dosed on TBW or ABW40. Maximum RRT associated with TEPA peak >1.75 μg/mL and combined thiotepa and TEPA AUC > 30 mg/h/L. 2 patients had detectable TEPA 6 d post dosing and had engraftment issues. Actual RRT not listed. −6 patients were > 120% IBW. Recommended dosing thiotepa at ABW40 because of lower RRT seen in obese patients.	[36]
Thiotepa	Dosed on TBW.	Single *adult* auto breast cancer patient (BMI 47) case report treated before 2002 (date not reported) with Cy 1000 mg/m^2/d plus thiotepa 80 mg/m^2/d plus carboplatin AUC 3.25/d for 4 d. PK drug values compared with normal population using PK targeting. Duration of follow-up not reported.	No specific toxicity or clinical data provided. Suggested dosing in obese patients with thiotepa on ABW 40-based BSA. Population data derived from HCT and non-HCT population data.	[52]
Antithymocyte globulin − equine or rabbit	Dosed onTBW.	Retrospective review of 61 *adult* and *pediatric* patients with SAA treated between 2006 and 2011 with an allo URD HCT on BMTCTN 0301 clinical trial at the 150 mg/kg level plus to ATG 3 mg/kg/d or 30 mg/kg/d for 3 d plus fludarabine 30 mg/m^2/d for 4 d plus TBI 200 cGy × 1.	Phase I trial resulted in 7 of 14 patient deaths. 2 of pulmonary failure, 2 of ARDS, 1 multiorgan failure, 1 cardiac failure, and 1 viral infection. Ages 9-61 (2 children and 5 adults). Weight parameters not shown.	[59]

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Agent	Dosing Basis	Patient Population	Comments	Reference
Antithymocyte globulin − rabbit	Dosed on TBW.	Phase I trial of 72 *adult* allo MMUD HCT Bu targeted levels 1, 2, or 3 dosed at 170 mg/m^2, 180 mg/m^2, or 220 mg/m^2/d respectively for 4 d targeting daily AUC of 6000 ± 600, 7500 ± 750, 9000 ± 900 μmol/min. Patients also received fludarabine 40 mg/m^2/d for 4 d plus ATG 3.25 mg/kg/d for 2 d. Minimum follow up of 10 mo.	No weight parameters provided. SOS/VOD was the DLT with 0 at level 1, 7% at level 2, and 100% at level 3. -No difference in NRM between levels 1 and 2.	[8]
Antithymocyte globulin − rabbit	Dosed on TBW.	70 *adult* allo patients with a variety of hematologic disease states and MDS treated between 1999 and 2001. Conditioned with Bu 3.2 mg/kg for 4 d plus Flu 50 mg/m^2 for 5 d plus ATG(r) 4.5 mg/kg over 3 d. Median follow-up 16 mo.	1 Bu seizure, 70% grade II stomatitis, 74% ALT increases with 1 SOS, no reporting of cognitive/neurotoxic effects of fludarabine. Mean daily Bu AUC of 4900-5000 μmol/min. No patient weight parameters reported.	[44]

ABW indicates adjusted body weight; ABW25, IBW + .25(TBW-IBW); ABW40, IBW + .4(TBW-IBW); ABW50, IBW + .5(TBW-IBW); allo, allogeneic; ALT, alanine aminotransferase; AML, acute myelogenous leukemia; AUC, area under the curve; auto, autologous; ATG, antithymocyte globulin; ATG(e), antithymocyte globulin equine; ATG(e)60, antithymocyte globulin equine 20 mg/kg/day for 3 days; ATG(r), antithymocyte globulin rabbit; BEAM, carmustine, etoposide, cytarabine, and melphalan; BMI, body mass index; BMTCTN, Blood and Marrow Transplant Clinical Trials Network; BSA, body surface area, Bu, busulfan; Bu16, busulfan 16 mg/kg PO over 4 days, Bu12.8, busulfan 12.8 mg/kg i.v. at variable dosing frequencies; BuCy2, busulfan 16 mg/kg Po plus Cy 120 mg/kg for 2 doses; cGy, centigray; C_{ss}, concentration at steady state; CML, chronic myelogenous leukemia; Cy, cyclophosphamide; Cy120, cyclophosphamide 120 mg/kg over 2 days; Cy200, cyclophosphamide 200 mg/kg over 4 days; d, day; DAH, diffuse alveolar hemorrhage; DFS, disease-free survival; DLT, dose-limiting toxicity; E, etoposide; ECP, extracorporeal photophoresis; Flu, fludarabine; FLU(150), Fludarabine 30 mg/m^2/day for 5 days; GFR, glomerular filtration rate; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant; IBW, ideal body weight; LFS, leukemia-free survival; LOS, length of stay; mg, milligram; MDS, myelodysplasia; MMUD, mismatched unrelated donor; MPD, myeloproliferative disorder; MRD, matched related donor; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; NRM, nonrelapse mortality; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PO, oral; PTLD, post-transplantation lymphoproliferative disorder; RRT, regimen-related toxicity; RIC, reduced-intensity conditioning; SAA, severe aplastic anemia; SOS, sinusoidal obstruction syndrome; TBI, total body irradiation; TBW, total body weight; TRM, treatment-related mortality; URD, unrelated donor; VOD, veno-occlusive disease.

When possible, early-phase studies were chosen to illustrate the doses associated with MTD and DLT to facilitate the assessment for known MTD when reviewing a new protocol. Combination regimens often result in different toxicity profiles and doses to achieve MTD and DLT than those in single-agent regimens. Monoclonal and polyclonal antibodies are generally dosed on TBW or given as a flat dose, and it is currently unknown if dosing on alternate body weights would provide either equal immune modulation or different toxicity risks. Study results and descriptions are brief and the original reference should be reviewed before protocol use to assess other aspects of care, specific drug product used, dose-specific parameters, nondosing related outcomes, and to ensure safe medication administration to patients.