

EDITORIAL

A time to stop, a time to start: high-dose chemotherapy in overweight and obese patients

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The prevalence of overweight and obesity in US adults exceeds 70%.¹ Their sometimes co-occurrence as well as their potential promoting association with malignancy has caused significant concern and controversy among research scientists and clinical oncologists, especially those responsible for treating patients with chemotherapy. Cancer chemotherapy is most commonly administered on a weight basis, calculated either directly per unit weight (pound or kg) or indirectly relative to body surface area (BSA; m²), which is determined on the basis of height and weight. These practices have evolved from observations such as that *in vitro* tumor cell killing is dose dependent, higher doses reduce emergence of resistant tumor cell clones and the use of weight and/or BSA-based dosing provides an approach to translate to humans effective doses determined in animals.^{2,3} Moreover, the success associated with high dose, compared with conventional, chemotherapy in hematolymphocytic malignancies provides strong support for the antitumor and the survival benefits of exposing tumors to high concentrations of chemotherapy.⁴

For overweight or obese cancer patients, the use of actual body weight or BSA for chemotherapy dose calculation will result in increased administration of cytotoxic agents relative to patients of normal weight. Because of the concerns that overweight or obese patients may have intrinsically compromised health status, adverse prognostic factors, altered pharmacokinetics and/or significantly impaired survival, and that increased doses of cytotoxic agents will cause greater toxicity, cancer chemotherapy in obese patients has frequently been administered on the basis of ideal weight rather than actual weight, or in some cases, at reduced doses.^{5–7} Unfortunately, these practices may compromise the curative potential of chemotherapeutic agents. An expert panel convened by the American Society of Clinical Oncology (ASCO) reviewed these concerns and the relevant literature, and concluded that the evidence was not sufficient to indicate the occurrence of short- or long-term toxicity among obese patients receiving full weight-based chemotherapy doses. For conventional chemotherapy, the panel recommended using full weight-based dosing, especially when the goal of treatment is cure.⁸

As noted above, the ASCO panel recommendation for full weight-based dosing was for conventional chemotherapy, whereas no recommendations were made for high-dose chemotherapy accompanied by hematopoietic stem cell transplant (HCT) interventions, where similar concerns and controversies exist regarding high-risk prognostic factors, and adverse effects in overweight and obese patients. As a result of these concerns, some patients who might benefit from high-dose therapy are prevented from receiving therapy altogether or they may receive reduced dosing relative to body mass. Although results for efficacy and tolerability of high-dose chemotherapy with HCT in overweight patients are inconsistent, the prevailing concept is that high-dose chemotherapy and HCT can be safely administered in overweight and obese patients without increased adverse effects or compromised outcomes.^{9–11} In a recent perspective, we recommended dosing on the basis of adjusted body weight (Adj

BW) to partially increase the dose relative to increased body mass and to then conduct studies to further increase dosing until full body weight is used as the basis for calculation, or dose-limiting toxicity is reached.¹² After a comprehensive literature review, the American Society of Blood and Marrow Transplantation Practice Guidelines Committee subsequently concluded that there was insufficient data to make evidence-based recommendations for how to dose high-dose chemotherapy in obese patients.¹³ They, however, provided a series of dosing recommendations for specific chemotherapeutic agents which for different agents were based on either total body weight (TBW) or Adj BW (ideal body weight (IBW) plus 25 or 40% of (TBW – IBW)) thus employing increased drug in proportion to weight.

In this issue of *Bone Marrow Transplantation*, Lau *et al.*¹⁴ report that the use of Adj BW to calculate the dose of chemotherapy did not adversely impact the outcome in obese lymphoma patients undergoing autologous stem cell transplant using BU, CY and etoposide as the myeloablative conditioning regimen. In fact, obese patients who presumably received the highest amounts of chemotherapeutic agents showed a decrease in 100-day mortality relative to normal or overweight patients, but no significant difference in relapse-free survival or OS.¹⁴

In this single-center, retrospective study of the safety and efficacy of auto-SCT in 476 adult lymphoma patients, all drugs were dosed on the basis of Adj BW in which 25% of the difference between TBW and IBW was added to the patient's IBW to determine Adj BW (Adj BW = IBW + 0.25 (TBW – IBW)), which was then used as the basis for dose calculations.

Compared with other sometimes contradictory reports, important advantages of this single-center report is its size, reporting on 472 patients, and the presumption that all anthropomorphic measurements, all dosing-based calculations and all other aspects of patient management and evaluation were performed in a consistent fashion.

In considering the results of this study, it is important to acknowledge that the goal of the intervention is tumor ablation, not myeloablation. Tumor ablation is expected to be dose dependent, whereas myeloablation is the life threatening severe toxic side effect, which is expected to be bypassed or circumvented by infusion of sufficient autologous stem cells to reconstitute the host hematopoietic capacity. Thus, the restoration of hematopoietic cell function with autologous stem cells is expected to be dependent on the number of infused stem cells and independent of administered drug dose. The efficacy of this approach in circumventing toxicity associated with adjustable weight dosing is clearly shown by the fact that days to recovery of absolute neutrophil count > 500 cells/μL and days to recovery of platelets > 20 000 cells/μL showed no statistical differences between normal/underweight, overweight and obese patients.

In terms of short-term toxicity to other organs, none of the weight-adjusted doses of chemotherapy caused sinusoidal obstructive syndrome, and there was no significant difference by weight group in mucositis score or severe mucositis. Secondary malignancy, a potential long-term toxicity that might be expected to increase with increasing doses of chemotherapy, showed no significant differences associated with weight in 5-year cumulative incidence, and there was no development of any unique type of malignancy.¹⁴

No specific anatomical or molecular markers of post-transplant residual tumor mass are available to determine specific antitumor effects of adjusted weight antitumor therapy. However, as the relapse rates in the three weight groups, at 1, 3 and 5 years, were not significantly different, these results suggest the probability that the increased drug dose associated with obesity was at least as effective in attaining the same degree of tumor control as the more standard dose given to normal weight patients. These results could be interpreted to suggest that drug based on ideal weight in the obese patients might have been inadequate to attain this same degree of tumor control.

On the basis of the results of several retrospective reviews of high-dose chemotherapy that were unable to provide convincing evidence to support the notion that high-dose therapy with HCT in overweight and obese patients is associated with adverse prognostic factors or worse outcomes, it is time to stop performing retrospective literature reviews and to start performing carefully monitored dose-escalation studies to provide overweight and obese patients with maximal drug dose to enhance possibility for complete tumor eradication and cure. For oncologists who remain concerned about full weight-based dosing, this goal could be approached by randomizing patients to dose escalation on the basis of Adj BW to include IBW plus 25, 50, 75 and 100% of the difference between IBW and TBW. Such studies should include careful monitoring of pharmacokinetics and clinical outcomes including antitumor effects, short- and long-term toxicities, time to relapse and OS.

The report in this issue by Lau *et al.*¹⁴ is a step in the right direction and provides a solid base that the floor for escalation of the BU, CY and etoposide regimen accompanied by autologous HCT in overweight and obese lymphoma patients should be dosed using Adj BW in which IBW is increased by 25% of difference between IBW and TBW. It needs to be emphasized that the results reported in this study are specific for the BU, CY and etoposide regimen and need to be independently established for other agents.

And although not the focus of this commentary, it is noteworthy that obesity is frequently accompanied by inactivity, which in itself is a risk factor for increased mortality.^{15,16} Accordingly, it is probable that the outcomes of high-dose chemotherapy in overweight and obese patients could be improved by institution of vigorous physical activity and exercise programs, before, during and after high-dose chemotherapy.^{17–19}

CONFLICT OF INTEREST

The author declares no conflict of interest.

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