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Chemotherapy dose in obese AML patients: to cap or not to cap?

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As of 2013, it is estimated that 2.1 billion people worldwide are overweight (body mass index, BMI, 25 or < 30 kg/m²) or obese (BMI ≥ 30 kg/m²), and one-third of the adult population in the United States is obese.¹ However, despite the rapid increase in obesity rates throughout the world over the past three decades, the effect of obesity on cancer outcomes and toxicity was mostly unknown until recently and remains poorly explored to date. Obesity is linked to a higher risk of developing cancer, and to a higher risk of cancer recurrence and mortality.^{2,3} It has been estimated that 90,000 deaths from cancer could be prevented annually in the United States if patients maintained a BMI < 25 kg/m².³ At this point, it is not known whether the increased mortality of obese patients with cancer is related to complications from co-morbidities such as diabetes and cardiovascular disease, to altered chemotherapy drug metabolism and pharmacodynamics, or to other unknown factors such as an obesity-related chronic inflammatory state.

In acute myeloid leukemia (AML), one might similarly expect that obese patients would have decreased tolerability of chemotherapy and worse outcomes during and after treatment. However, contrary to the findings in other types of cancer, several recent retrospective analyses demonstrate an apparent lack of significant increase in chemotherapy-related toxicity for obese patients compared to non-obese patients receiving standard therapy for AML according to actual body weight (instead of ideal body weight or capped at body surface area of 2 m²), in addition to similar and/or improved clinical outcomes, measured as complete remission (CR) rates and overall survival (OS).

Still, an unanswered clinical question remains for this cohort: What is the optimal dosing strategy for obese AML patients undergoing conventional induction chemotherapy? The largest study to report specifically on the effect of obesity on outcomes in AML examined a retrospective cohort of nearly 2000 patients treated on ten consecutive experimental protocols through the Southwestern Oncology Group (SWOG).⁴ No dose adjustments were made, and obese AML patients had higher CR rates and no increased chemotherapy toxicity (Table 1). Similar findings have been observed in single-institution cohorts where patients

received chemotherapy dosed according to actual body weight or calculated body surface area (BSA) without dose reductions or capping. In fact, one single-institution analysis suggested that the CR rate may be lower in obese patients when chemotherapy doses are capped based on BSA of 2 m^2 .^{5–8}

To date, these retrospective cohort studies suggest that chemotherapy should be dosed according to actual body weight (and not capped) for obese AML patients. Accompanying this editorial, Kempf and colleagues attempted to address whether chemotherapy dose capping impacted the outcomes of obese patients with AML undergoing conventional induction chemotherapy. For this, the authors initially asked whether BMI is independently associated with worse outcomes in AML patients. Next, the investigators determined whether capping the chemotherapy dose at a BSA of 2 m^2 was associated with worse outcomes. For their analyses, the investigators used a cohort of 233 newly diagnosed AML patients treated at a single institution over a decade (2003–2013). Of note, only 10% of the patients included in their study were obese (BMI ≥ 30). The authors determined that BMI was not independently associated with differences in CR rate, progression-free survival (PFS), or OS. They further examined 35 patients with BSA $\geq 2 \text{ m}^2$ who received capped chemotherapy dosing; again, no differences were found in CR rate, PFS, or OS.

Kempf and colleagues must be applauded for their efforts, though some limitations to the study design deserve to be highlighted. First, these are observations derived from a retrospective single-institution analysis. It is not completely clear why only a small percentage of the patients included were obese (10%, 23 patients) and overweight or obese (42%, 99 patients). These percentages are significantly lower than reported incidence of obesity in the French population (19.3% and 55.9% respectively) and contrast sharply to the rates of obesity previously reported in AML (Table 1).¹ Additionally, though BMI and BSA are not always directly correlated, only 35 patients (15%) had a BSA $\geq 2 \text{ m}^2$ in the study population, suggesting that sampling bias may have affected their results. This cohort of 35 patients received capped chemotherapy dosing and had no significant difference in CR rate, PFS, or OS compared to the patients with BSA $< 2 \text{ m}^2$ (who did not have a dosing cap); however, the authors did not explore whether differences in outcomes could be observed in the high-BSA population to the overweight/obese subset of patients with a BSA $< 2 \text{ m}^2$. Finally, the two study cohorts were not completely balanced for their baseline characteristics. For example, the obese and high BSA subsets had more favorable characteristics than the entire study cohort, including lower rates of adverse cytogenetic risk and secondary AML, and younger median age at diagnosis. Perhaps partially due to these population differences, the obese patients in this study did not have the improved outcomes observed in previous studies. Additionally, Kempf et al. did not report on chemotherapy toxicity, though prior studies have suggested that there is no significant difference in toxicity between obese and non-obese populations even when chemotherapy dose is not capped (Table 1).

Though the current study by Kempf and colleagues suggests that dose-capping may not be deleterious in patients with a high BSA, these results need to be interpreted with caution and may not be applicable to populations with different anthropomorphic features, such as low rates of obesity but tall stature, and therefore high BSA.¹ In addition, the American Society

of Clinical Oncology practice guidelines state that obese patients should receive full weight-based chemotherapy doses.⁹ Though the optimal dosing strategy for chemotherapy drugs for obese AML patients can only be conclusively answered through a randomized controlled trial, we suggest that full weight-based doses of chemotherapy should be given to AML patients with high BMI and/or high BSA.

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Summary of studies examining effect of obesity (BMI 30) on outcomes in patients with AML. All columns refer to obese patients only unless otherwise specified. NR = not reported; MVA = multivariate analysis

Table 1

Study	Study population, n	Number obese (%)	Cytogenetics	Rate of CR	Overall Survival	Chemotherapy toxicity	Other comments/conclusions
Kempf E et al, 2014	233	23 (10)	14% favorable 62% intermediate 24% adverse	No significant differences ¹	51% vs. 52% for normal weight at 3 years	NR	35 patients had chemotherapy doses capped at BSA 2m ² , and no significant differences found in CR, DFS, or OS
Medeiros, BC et al, 2012	1974	(25)	30% favorable 25% intermed 21% adv w/o MK 27% adv w/MK ²	55-61% vs. 52% for normal weight ³	17-26% ⁴ vs. 18% for normal weight at 5 years	No significant differences	MVA showed class I and III obesity statistically significantly associated with higher rate of CR and lower rate of resistant disease
Lee, HJ et al, 2012	329	104 (31.6)	10% favorable 41% intermediate 36% adverse	NR	15.4% at 5 years; mean 41.0 months vs. 36.5 months for normal weight	No significant differences	conclusion: dose chemotherapy at ABW
Wenzell, CM et al, 2013	247	85 (34)	13.4% favorable 45.3% intermed 27.1% adv	76.5% vs. 69.1% for under/normal weight	Median 14.2 months vs. 10.7 months for under/normal weight	No significant differences	conclusion: dose chemotherapy at ABW
Brunner, AM et al, 2013	97	31 (32)	NR	NR	Median 587 days vs. 215 days for under/normal weight	NR	Patients all > 60 years; statistically significant improved OS with increased BMI
Lin, A et al, 2013	63	21 (33) ⁵	28.6 favorable 47.6% intermed 5% adverse	81% vs. 69% in non-obese	NR; no significant difference compared to non-obese	No significant differences	Conclusion: dose reductions did not results in significantly different CR rates

¹ CR rate not reported for obese patient subgroup but was 82% overall. CR rates did not differ based on BMI.

² No significant association between BMT and karyotype

³ CR rates varied by obesity class: class I 55%, class II 61%, class III 60%. Differences were not statistically significantly different.

⁴ OS varied by obesity class: class I 19%, class II 17%, class III 26%. Differences were not statistically significantly different.

⁵ Classified patients as obese based on > 130% IBW.