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# Tolerability of Induction Chemotherapy Dosing Practices in Acute Myeloid Leukemia Patients

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## Abstract

For patients with high body surface areas (BSA), differing chemotherapy dosing strategies have been utilized in attempts to reduce toxicity. In a retrospective evaluation, we compared the effects of chemotherapy dosing in acute myeloid leukemia patients with high BSA (>2 $m^2$) who received capped doses ($n$ = 12) to those who received uncapped doses ($n$ = 24), and to patients with BSA $\leq$ 2 $m^2$ ($n$ = 42). There were no statistically significant differences among groups (BSA $\leq$ 2 $m^2$, BSA > 2 $m^2$ capped, and BSA > 2 $m^2$ uncapped) in the incidences of febrile neutropenia (85.7, 66.7, and 75.0%, respectively, $p$ = 0.29), bacteremia (19.0, 8.3, and 16.7%, respectively, $p$ = 0.68), mucositis (42.8, 50.0, and 41.7%, respectively, $p$ = 0.88) or nausea/vomiting (47.6, 33.3, and 37.5, respectively, $p$ = 0.57). Results suggest delivery of unadjusted chemotherapy based on actual body weight is likely safe in hematological malignancies.

## 1. Introduction

Chemotherapy agents are known to have narrow therapeutic indices, where a small difference in dose could potentially lead to poor treatment outcomes or increased toxicity [1], [2], [3] and [4]. This makes dose selection challenging, especially since many of the variable patient-related factors affecting the metabolism and clearance of these drugs are difficult to predict [3], [5] and [6]. It is often assumed that larger patients require higher doses than smaller patients to provide similar drug concentrations and outcomes [4]. Body surface area (BSA) has traditionally been and remains the most frequent measure used to determine chemotherapy doses [7], [8] and [9]. This method of dosing leads to difficulties when heights and/or weights are at extremes [3] and [6]. Given the rise in prevalence of obesity worldwide over the past few decades [10], selecting doses in this group is a common struggle due to concerns for potential toxicity associated with larger doses of chemotherapy when actual body weight is used to determine dosing. Thus, various dosing strategies for the obese population have been utilized amongst practicing physicians and institutions [11], [12] and [13]. Some of these include use of an adjusted body weight, ideal body weight, or capping the BSA at 2 $m^2$[4], [11], [12], [13], [14] and [15]. As result of this empiric weight modification, up to 40% of obese patients have received intentionally reduced chemotherapy dosages in an attempt to reduce the potential toxic effects [16].

In an attempt to clarify dosing strategies for clinicians, the American Society of Clinical Oncology (ASCO) developed a clinical guideline in April 2012, recommending the use of full-dose chemotherapy based on actual body weight for obese cancer patients specifically when the treatment goal is cure of the disease [17]. However, the guideline recommendations are based on studies in solid tumor malignancies and did not include obese patients receiving therapy for hematological malignancies. Patient weight in the leukemic population has been assessed in multiple studies in terms of impact on survival and toxicity; however, empiric dosing strategies to mitigate patient risk for toxicity (dose capping) has only been evaluated in one prior study [18], [19], [20] and [21]. The purpose of this study was to evaluate chemotherapy dosing in adult acute myeloid leukemia (AML) patients receiving induction treatment and determine if there are differences in toxicities when doses in patients with BSA > 2 $m^2$ are empirically capped, compared to when they are not capped, and to patients with BSA values ≤2 $m^2$.

## 2. Methods

### 2.1. Study patients

This retrospective, single center study was approved by the local Institutional Review Board. Adult patients with a diagnosis of AML that completed standard induction chemotherapy consisting of an anthracycline (idarubicin or daunorubicin) daily for 3 days in combination with continuous infusion cytarabine for 7 days between January 2008 and August 2013 were included in the study. Patients whom received radiation therapy or were pregnant during therapy were excluded.

### 2.2. Data collection and analysis

Demographic and clinical characteristics were collected from the electronic health record for all eligible patients, which included age, sex, height, weight, and calculated BSA value.

Chemotherapy agents and their respective doses administered, in addition to whether G-CSF was used during patients' hospital stay were also identified.

The following adverse effects were collected: episodes of febrile neutropenia, documented mucositis, documented bacteremia, and documented nausea and vomiting. Additional outcomes such as day of neutrophil recovery (ANC > 500 cell/mcL) post chemotherapy, length of hospital stay, and attainment of complete remission post induction chemotherapy as defined by the International Working Group (IWG) criteria (bone marrow blasts < 5%, ANC > 1000 $mcL^{-1}$, platelet count > 100,000 $mcL^{-1}$), were also collected [22].

BSA values were calculated based on patient height and weight using the Mosteller formula, $([\text{height (cm)} \times \text{weight (kg)}]/3600)^{1/2}$[9]. Patients were categorized into three groups based on their calculated BSA and the BSA utilized to dose the patient: those with BSA > 2 $m^2$ whom received empirically capped chemotherapy doses (capped group), those with BSA > 2 $m^2$ whom received full actual body weight calculated doses (uncapped group), and those with BSA ≤ 2 $m^2$. The BSA > 2 $m^2$ capped group was compared to both the BSA > 2 $m^2$ uncapped group, and to the BSA ≤ 2 $m^2$ group. The BSA > 2 $m^2$ uncapped group was also compared to the BSA ≤ 2 $m^2$ group.

### 2.3. Outcome measures

The primary end point was the overall incidence of adverse effects during admission, which included: occurrence of febrile neutropenia, documented mucositis, documented bactermia, and documented episodes of nausea or vomiting. Secondary endpoints were time (days) to neutrophil recovery (ANC > 500 cells/mcL) after the start of chemotherapy, length of hospital stay, and complete remission following induction chemotherapy.

### 2.4. Statistical methods

Continuous variables between groups were compared using Student's *t*-test (or non parametric Mann–Whitney *U* tests, dependent upon the parametric nature of the data). Categorical data was compared between groups using a Fisher's exact test or a Pearson chi-square test, as appropriate. These analyses were performed using SPSS 21.0 (Statistical Package for the Social Sciences, Chicago, IL). A two sided *p*-value <0.05 was considered significant. Univariate comparisons on demographic and clinical variables were made to assess the comparability between the three groups. Incidences of adverse effects were analyzed univariately using Fisher's exact tests. Binary logistic regression analyses were used to obtain adjusted odds ratios of the significant predictors of adverse events and the attainment of complete remission following induction chemotherapy. Predictors accounted for in the regression included BSA, dosing strategy (capped/uncapped), sex, age, history of prior chemotherapy, receipt of granulocyte-colony stimulating factor and chemotherapy agent (daunorubicin/idarubicin). Time to neutrophil recovery and hospital lengths of stay were analyzed using Kaplan Meier survival analysis and Cox regression.

## 3. Results

### 3.1. Baseline and treatment characteristics

Of the 78 patients included in the evaluation, 42 had a BSA ≤ 2 $m^2$, 24 had a BSA > 2 $m^2$ and received uncapped actual body weight (ABW) calculated doses, and 12 had BSA values >2 $m^2$ and received capped doses. Patient demographics and treatment characteristics are provided in Table 1. Excluding the expected differences in average weight, height and BSA, there were no significant differences in patient characteristics between the groups except for gender. A higher proportion of patients were male in the BSA > 2 $m^2$ groups. The average age of all evaluated patients was 56.5 years and few patients (10.3%) had previous chemotherapy exposure. All patients completed standard induction chemotherapy with an anthracycline and cytarabine. The type of anthracycline agent received and dosages (daunorubicin, 30–90 mg/$m^2$; idarubicin, 12 mg/$m^2$; cytarabine 100–200 mg/$m^2$) were not different among the groups. The actual capped dose administered to patients with a BSA > 2 was on average 10.5% lower for idarubicin, 13.3% lower for daunorubicin, and 11.4% lower for cytarabine then they would have been had their doses been uncapped.

**Table 1. Baseline and treatment characteristics.**

| | **BSA ≤ 2 $m^2$ (*n* = 42)** | **BSA > 2 $m^2$ capped (*n* = 12)** | **BSA > 2 $m^2$ uncapped (*n* = 24)** | ***p*-Value** |
|---|---|---|---|---|
| Mean age (years) | 58.9 | 53.8 | 53.7 | 0.61 |
| Male, *n* (%) | 15 (35.7) | 8 (66.7) | 18 (75) | 0.005 |
| Mean BSA, $m^2$ (range) | 1.78 (1.45–1.98) | 2.25 (2.05–2.85) | 2.20 (2.02–2.73) | 0.001* |
| Mean weight (kg) | 70.3 | 107.9 | 100.6 | 0.001* |
| Mean height (cm) | 165.2 | 176.8 | 178.6 | 0.001* |
| Previous chemotherapy exposure, *n* (%) | 3 (7.1) | 2 (16.2) | 3 (12.5) | 0.57 |
| Receipt of granulocyte colony stimulating factor (G-CSF), *n* (%) | 12 (28.6) | 1 (8.3) | 9 (37.5) | 0.19 |
| Median daunorubicin dosage (mg/$m^2$) [IQR] | 60 [45.0] | 52.5 [32.5] | 60 [20.0] | 0.98 |
| Median idarubicin dosage (mg/$m^2$) [IQR] | 12 [0] | 12 [0] | 12 [0] | 1.00 |
| Median cytarabine dosage (mg/$m^2$) [IQR] | 100 [100] | 100 [100] | 100 [100] | 0.74 |

BSA: body surface area, IQR: interquartile range.

*Statistically significant difference between BSA ≤ 2 $m^2$ and BSA > 2 $m^2$ groups. No statistically significant difference between BSA > 2 capped and BSA > 2 uncapped groups in BSA ($p$ = 0.36), weight ($p$ = 0.21), and height ($p$ = 0.54).

### 3.2. Outcomes

There were no significant differences in rates of chemotherapy related adverse effects among patients with BSA $\leq 2$ m$^2$, BSA $> 2$ m$^2$ that received capped doses, and BSA $> 2$ m$^2$ that received uncapped doses (Table 2). The most common adverse effect was febrile neutropenia, which occurred in 85.7%, 66.7% and 75.0% ($p = 0.29$) of patients, respectively. Thirteen of the 78 patients (16.7%) had documented bacteremia during their admission with no significant difference in incidence among the groups (19.0%, 8.3%, 16.7; $p = 0.68$). The rates of documented mucositis were similar between groups ($p = 0.88$), affecting 42.8% of patients in the BSA $\leq 2$ m$^2$ group, 50.0% in the BSA $> 2$ m$^2$ capped group, and 41.7% in the BSA $> 2$ m$^2$ uncapped group. The reported incidence of nausea and/or vomiting was 47.6%, 33.3%, and 37.5%, respectively ($p = 0.57$).

**Table 2. Incidence of adverse effects.**

| | **BSA $\leq 2$ m$^2$ (*n* = 42)** | **BSA $> 2$ m$^2$ capped (*n* = 12)** | **BSA $> 2$ m$^2$ uncapped (*n* = 24)** | ***p*-Value** |
|---|---|---|---|---|
| Febrile neutropenia, *n* (%) | 36 (85.7) | 8 (66.7) | 18 (75.0) | 0.29 |
| Nausea/vomiting, *n* (%) | 20 (47.6) | 4 (33.3) | 9 (37.5) | 0.57 |
| Mucositis, *n* (%) | 18 (42.8) | 6 (50.0) | 10 (41.7) | 0.88 |
| Bacteremia, *n* (%) | 8 (19.0) | 1 (8.3) | 4 (16.7) | 0.68 |
| Median time to ANC > 500 cells/mcL (days) | 25.5 | 24.5 | 29.5 | 0.48 |
| Median length of hospitalization, days | 31.5 | 27.5 | 35.0 | 0.34 |
| **Complete remission (CR)** | | | | |
| Number evaulable | 37 | 10 | 22 | |
| CR, *n* (%) | 17 (45.9) | 7 (70.0) | 11 (50%) | 0.4 |

BSA: body surface area, ANC: absolute neutrophil count, std. dev: standard deviation.

The mean time to neutrophil recovery was longest for the patients that received uncapped doses, but not significantly different ($p = 0.48$) among the three groups (Fig. 1). It took a median of 25.5 days for patients with BSA $\leq 2$ m$^2$ to recover their neutrophils compared to 24.5 days for those with BSA $> 2$ m$^2$ that received capped doses and 29.5 days for those with BSA $> 2$ m$^2$ that received uncapped doses. Median length of hospital stay did not significantly differ among the three groups (31.5 days, 27.5 days, 35.0 days, respectively, $p = 0.34$).

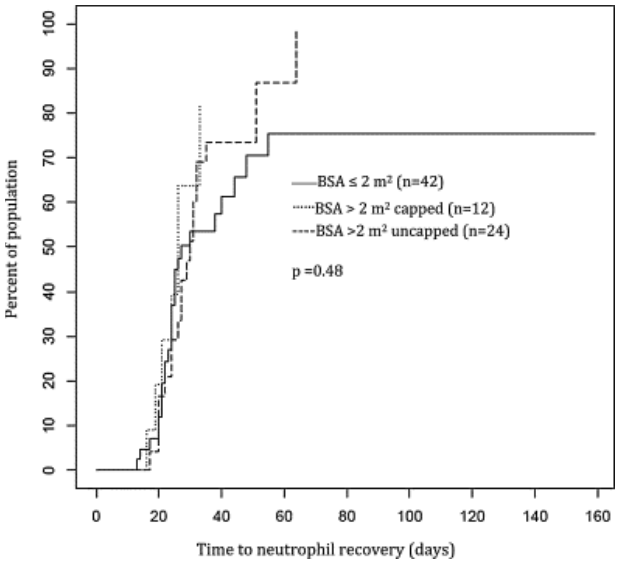


**Fig. 1. Days to neutrophil recovery post induction chemotherapy.**

Based on the post-induction analysis of complete remission (CR), there was no significant difference in the incidence of CR among all the groups. Of the 37 patients in the BSA $\leq 2$ $m^2$ group evaluable for response, 17 (45.0%) achieved a CR. Similarly, 50.0% of patients with BSA > 2 $m^2$ that received uncapped doses (22 evaluable patients) and 70.0% of those that received capped doses (10 evaluable patients) achieved a CR. In total, 5 patients experienced early death (prior to assessment of response).

Utilizing multivariate analysis, BSA and dosing strategy (capped/uncapped) were not found to be significantly associated with toxicity rates (febrile neutropenia, bacteremia, mucositis, nausea/vomiting) or post-induction complete remission rate. Age was the only significant predictor of nausea/vomiting (odds ratio 0.96, 95% CI 0.92–0.99, $p = 0.02$).

## 4. Discussion

As the prevalence of obesity continues to increase worldwide [10], clinicians will likely encounter a greater proportion of cancer patients with high BSA values. Determining the most appropriate strategy for dosing chemotherapy in this population is important to ensure effective treatment while avoiding unnecessary toxicities.

Much of the current knowledge of dosing practices and chemotherapy toxicity effects in obesity is based on evidence in breast cancer. However, a few studies are available in the leukemic population in which body weight has been reported to effect outcomes. A study of 97 adults with AML over the age of 60 years investigated the association between baseline BMI and overall survival [19]. Patients with a BMI greater than 30 had a lower hazard ratio for mortality compared to those with a BMI less than 25 (HR 2.14; 95% CI 1.21 to 3.77). Patients in this study were dosed based on actual body weight without any dose reductions in the obese population. Similarly, a study of 1974 adult patients with AML showed CR rates were higher with increasing BMI (OR 1.03, $p = 0.004$) and that there was no association between toxicity and BMI [20]. Patients were treated with doses based on actual BSA (one patient received treatment based on ideal body

weight). In yet another study ($n$ = 247), the toxicity and efficacy of actual body weight based chemotherapy doses were compared amongst underweight/normal (BMI < 18.5–24.9 kg/m$^2$), overweight (BMI 25–29 kg/m$^2$), and obese (BMI > 30 kg/m$^2$) AML patients that received standard induction treatment [18]. Results showed no significant differences in toxicity, including days to neutrophil recovery, incidence of documented bacteremia and heart failure among normal, overweight and obese patient groups. In addition, complete remission rates were also similar among the groups. Authors concluded that use of full actual body weight based doses is justified even at extremes of weight. Overall, these assessments were based on patients who received non-dose reduced chemotherapy regimens and excluded those with empirically adjusted doses.

One study investigating the impact of obesity on the efficacy and toxicity of induction chemotherapy in AML patients ($n$ = 63) did describe the impact of dose reduction in the obese population [21]. Obesity was defined as ≥30% above ideal body weight. Seven of the 21 obese patients received a dose reduction (1 was reduced for renal impairment, 4 used an adjusted weight BSA, and 2 capped the BSA at 2). No differences were identified in toxicity between those receiving a dose reduction and those receiving unreduced doses based on actual body weight. Additionally, there was no association in the total population between obesity and toxicity, including neutrophil recovery by 30 days (OR 1.11, $p$ = 0.43) and platelet recovery by 30 days (OR 1.12, $p$ = 0.36).

Our evaluation showed similar results, although patients were analyzed based on their BSA and respective dosing strategy used, rather than BMI or precent above ideal body weight. We found no significant differences in the incidences of any of the evaluated chemotherapy related adverse effects, time to neutrophil recovery, or lengths of hospitalization among patients with BSA ≤ 2 m$^2$, those with BSA > 2 m$^2$ that received uncapped doses, and those with BSA > 2 m$^2$ that received intentionally capped doses. Additionally, assessment of response to determine efficacy of the received induction therapy demonstrated no differences in rates of CR after bone marrow recovery between the groups.

Interestingly, patients with BSA ≤ 2 m$^2$ experienced a greater incidence (though non-significant) of febrile neutropenia, nausea/vomiting, and documented bacteremia than patients with BSA > 2 m$^2$ regardless of dosing strategy used. Similar results have been shown in previous studies performed in breast cancer patients suggesting larger patients may be underdosed even with full, actual body weight based doses [1] and [13].

Overall, our patient population recovered their neutrophils a few days sooner than the previous study of AML patients (27.3 vs 33.0 days, respectively) [20]. Although not statistically significant, it took slightly longer to recover neutrophil counts for those patients that received uncapped doses (29.6 days) implying a possible greater myelotoxic effect compared to those who received capped doses and those with BSA ≤ 2 m$^2$ (23.6 and 26.7 days), respectively. However, there was no correlation with neutrophil recovery time and average length of hospitalization as patients in the BSA ≤ 2 m$^2$ group recovered their counts sooner than the uncapped group, but had a non-significant longer hospital stay.

Limitations include the retrospective design of the study as some patients had incomplete and/or missing data if they received follow-up outside the institution. Though analysis of the data showed

that there were no significant differences between groups, the results may be limited by the small sample size and may lack the power to detect more minute differences. Most importantly, prognostic factors were not taken into account when assessing response, making efficacy difficult to assess and compare across groups. In addition, the primary outcome was the incidence of adverse effects, which relied on physician interpretation and documentation in the medical record.

## 5. Conclusion

The use of ABW based doses in patients with BSA > 2 $m^2$ was not associated with an increase in toxicity as there were no significant differences in the incidence of adverse effects among the BSA > 2 $m^2$ capped, BSA > 2 $m^2$ uncapped, and BSA ≤ 2 $m^2$ groups. Attempts to reduce toxicity by empirically reducing chemotherapy doses for patients with high BSA values may not be justified as no significant benefit was seen in regard to toxicity or neutrophil recovery in patients with BSA > 2 $m^2$ who received capped doses. These results further support the safety of ASCO recommendations for the use of uncapped/unadjusted chemotherapy doses in the hematological malignancy setting.

## Conflict of interest statement

The authors do not have any conflicts of interest to disclose.


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