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Influence of Obesity on Efficacy and Toxicity of Induction Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia

Andrew Lin^{1,*}, Megan Othus², Amy McQuary¹, Mary Chi¹, and Elihu Estey^{1,2}

¹University of Washington Medical Center, Seattle, WA

²Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract

Background—Increased body mass index (BMI) is associated with increased risk of treatment-related complications and inferior overall survival in children and adolescents with AML. The growing proportion of the general population who are obese raises the dilemma of whether the pharmacokinetic differences in obese patients necessitate chemotherapy dosage adjustments. This also poses the question of whether obese patients experience differing outcomes or toxicities with chemotherapy.

Objective—We are retrospectively evaluating the association between percentage of ideal body weight (IBW) and complete remission (CR) among newly diagnosed, previously untreated AML patients. We also describe secondary objectives including associations between IBW and overall survival (OS), platelet and neutrophil recovery, and incidence of grade 3-4 hematologic and nonhematologic toxic effects. Additionally, we characterize the dosing strategies used for induction chemotherapy in obese patients with AML at a single institution.

Methods—This is a retrospective study of obesity and its impact on outcome in 63 newly diagnosed, previously untreated adults with AML receiving standard induction chemotherapy with 7 + 3 from 2006 to 2010.

Results—The median percentage of ideal body weight was 121% (range 86-246%). Thirty-five percent of patients were obese (> 130% IBW). Controlling for history of prior malignancies, FLT3-ITD status, and NPM1, obesity was not associated with CR (odds ratio [OR] = 0.97, p=0.88), OS (hazard ratio=0.48, p=0.52), platelet recovery by 30 days (OR=1.14, p=0.52), or neutrophil recovery by 30 days (OR=1.12, p=0.60). Among obese patients, CR rates were not significantly different comparing patients not dose adjusted to patients with obesity-related adjustments (CR=86% vs. 67%, p=0.55)

Conclusion—In this study population, obesity was not an independent prognostic factor of outcome or toxicity. Empiric dose reductions based on obesity did not result in significantly different CR rates.

*Correspondence: Andrew Lin, PharmD, University of Washington Medical Center, 1959 NE Pacific St, Box 356015, Seattle, WA 98195, Ph: 704-617-3420, andrew.p.lin@gmail.com.

Keywords

acute myeloid leukemia; obesity; outcome

Introduction

Many variables, most obviously whether therapy is successful in producing a response and the duration of that response affect the survival of patients with acute myeloid leukemia (AML). Currently, idarubicin (12 mg/m²/day) or daunorubicin (45, 60, or 90 mg/m²/day) for three days plus cytarabine (100-200 mg/m²/day) for seven days, or “7+3”, is a standard induction therapy for patients with newly diagnosed AML.¹ Factors influencing response to this type of treatment include genetic factors (i.e. unfavorable karyotype or FLT3-ITD positivity), older age, hyperleukocytosis, history of previous hematologic disorder, prior chemotherapy, and poor performance status.²

Obesity has increased to epidemic proportions, with 32.2% of US adults age 20 years or older classified as obese (body mass index [BMI] ≥ 30 mg/m²).³ A 2007 meta-analysis reported the relative risk for the development of leukemia is increased in overweight (BMI 25-29.9) and obese (BMI ≥ 30) individuals. On a continuous scale, a 5 kg/m² increase in BMI was associated with a 13% increased risk of leukemia (RR, 1.13; 95% CI, 1.07–1.19).⁴ In addition, obesity increases the occurrence of co-morbidities that may complicate treatment and in children with AML obesity has been identified as a factor predictive of inferior survival.^{5, 6, 7} Reports in adults with the subtype of AML, acute promyelocytic leukemia also indicate obese patients to be at greater risk of treatment-related toxicities.⁸ Obesity also affects chemotherapy pharmacokinetics as obese patients have increased fat percentage and altered regional blood flow affecting volume of distribution, clearance, and consequent drug exposure.^{9, 10}

The potential importance of obesity has increased given recent investigations demonstrating that higher doses of daunorubicin results in higher response rates (RR) and improved overall survival without significant increases in toxicity in patients up to age 65.^{11, 12} However, the risk of these dosing strategies in obese patients is unknown, and the possibility of overdosing them exists.

A primary purpose of this work is to characterize the dosing strategies used at the University of Washington Medical Center (UWMC) with induction chemotherapy for obese patients with AML and assess the evidence that supports arbitrary dose reductions in the obese. Overall, obesity is associated with increased cancer-related mortality, even when controlling for other variables.¹³ However, there is concern that empiric dose reduction of chemotherapy could contribute to poorer response rates in obese patients. The intent of this investigation is to retrospectively investigate the impact of obesity on the percentage of patients with newly diagnosed AML achieving CR with induction chemotherapy with 7+ 3. Secondly we hope to describe disease-free survival (DFS), overall survival (OS), and safety as described by the incidence of grade 3 and 4 hematologic and nonhematologic toxicities between obese and non-obese patients.

Methods

Patients

A retrospective, single center chart review identified adults with newly diagnosed, previously untreated AML who received 7 + 3 induction chemotherapy, without adjuvants such as gemtuzumab ozogamicin, from January 2006 to January 2010. Ideal body weight was calculated using standard formulas seen in figure 1. Percent above ideal body weight (IBW) was calculated using height and weight at time of initiation of therapy. Patients were classified as obese in this study if they were $\geq 130\%$ of their IBW and non-obese otherwise as consistent with current practice when dose reducing for obesity in chemotherapy.¹⁴ Cytogenetic data was collected from time of diagnosis and stratified according to MRC criteria.^{15, 16} The University of Washington institutional review board approved this study.

Statistical analysis

Complete remission (CR) was defined as bone marrow blasts $< 5\%$; absence of blasts with Auer rods; extramedullary disease; and recovery of absolute neutrophil and platelet counts to $> 1,000$ and $> 100,000$ per microliter respectively. Minimal residual disease (MRD) was said to be present if flow cytometry showed $> 0.01\%$ immunophenotypically abnormal blasts despite the presence of CR. Neutrophil recovery was defined as absolute neutrophil count recovery to $> 0.5 \times 10^9/\text{L}$ by day 30. Platelet recovery was defined as platelet count $> 50 \times 10^9/\text{L}$ by day 30 and independence of platelet transfusions. Overall survival (OS) was measured from the date of start of induction chemotherapy until death from any cause, with observation censored at the date of last contact for patients lost to follow up. Hematologic and nonhematologic toxicities were graded according to the NCI Common Technology Criteria for Adverse Effects v4.0 (CTCAE).

Fisher's exact test evaluated associations between categorical variables (e.g., to compare complete response between the obese and non-obese groups). The Kruskal-Wallis test was used to test medians of numerical variables such as age between groups. Cox proportional hazards models assessed associations with the outcome OS. Logistic regression models assessed associations with the outcomes CR, neutrophil recovery at 30 days, and platelet recovery at 30 days. All reported p-values are two-sided. P-values < 0.05 were deemed statistically significant.

Results

Baseline characteristics of the patients (Table 1)

We identified 63 patients who received 7 + 3. The median age in the cohort was 55 (range 22-75). The median percentage of ideal body weight (IBW) was 121% (range 86-246%) and 35% of subjects were obese ($\geq 130\%$ IBW). There were no significant differences between the obese and non-obese subjects, except for gender. A larger proportion of females were obese (60% vs. 9%, $p < 0.01$).

Dosing strategies and outcomes (Figure 2)

In 7 of 21 obese patients dose reductions were applied, however one patient received dose adjustment due to renal dysfunction. The method most commonly applied was to calculate an adjusted body surface area (AdjBSA) based off adjusted body weight. The rationales for dose reductions were typically not documented. The obese subjects who received a dose adjustment were on average younger and had a higher BMI. There were no significant differences between groups in cytogenetics, FLT-3, or NPM-1 status (Table 2). The CR rate was 4/6 (67%) in dose-reduced obese patients vs. 12/14 (85.7%) in obese patients whose dose was not reduced. There was no significant difference in toxicity between obese patients who received an empiric dose reduction compared to those that did.

Univariate association of obesity with CR, OS, and MRD

Non-obese subjects had a CR rate of 69% (29/42) versus 81% (17/21) of obese patients, however the difference was not statistically significant ($p=0.26$). There was no significant difference between the CR rates of obese patients who had a dose adjustment versus those who did not (67% for dose adjustment, 86% for no dose adjustment, $p=0.55$). Table 3 summarizes univariate associations with CR. None of the factors considered was significantly associated with CR. Obesity was not associated with decreased OS (hazard ratio [HR] 0.26, $p = 0.08$) or increased risk of minimal residual disease (odds ratio [OR] 0.81, $p = 0.11$).

Univariate association of obesity and toxicity

There was no significant association between obesity and toxicity. There was no significant association between obesity and neutrophil recovery by 30 days (OR 1.11, $p = 0.43$) or platelet recovery by 30 days (OR 1.12, $p = 0.36$). All but one patient in our study sample experienced neutropenic fever.

Univariate association of other prognostic factors with study outcomes

Cytogenetic risk category was significantly associated with MRD ($p=0.03$), platelet recovery by day 30 ($p=0.002$), and neutrophil recovery by day 30 ($p=0.01$). As one might expect, patients in our study with good cytogenetics had better outcomes compared to patients with poor prognosis cytogenetics. Figure 3 shows the proportion of patients who recovered platelets and neutrophils by day 30 by cytogenetic risk category. A history of previous malignancy was also associated with increased risk of MRD ($p=0.02$) and decreased platelet recovery by day 30 ($p=0.01$), and neutrophil recovery by day 30 ($p=0.01$).

Multivariate analysis of obesity

Controlling for history of prior malignancy, FLT3-ITD status, and NPM-1, obesity continued to not be significantly associated with CR (OR=0.97, $p=0.88$). This was also the case when only controlling for cytogenetic risk category (OR=1.12, $p=0.35$). Controlling for history of prior malignancy, FLT3-ITD status, and NPM-1, platelet recovery by 30 days was not associated with CR (OR=1.14, $p=0.52$), nor was neutrophil recovery by 30 days (OR=1.12, $p=0.60$).

Discussion

In 2005, the World Health Organization (WHO) estimated that approximately 1.6 billion adults were overweight and at least one-quarter of these were obese. By 2015, these numbers are expected to be 2.3 billion and 700 million, respectively.¹⁶ This problem is even more pronounced in the United States as in 2003-2004 32.2% of US adults age 20 years or older classified as obese (BMI ≥ 30 mg/m²).³ In the general population, being overweight and/or obese has been associated with increased mortality. Although a large proportion of this increased mortality is attributable to cardiovascular-related deaths the risk of mortality due to cancer was also increased in the obese population compared to those of normal weight (reference category: BMI 22.5 – 24.9).¹⁶ Interestingly, obesity has also been shown to be associated with an increase in the incidence of several cancers. Noteworthy amongst these is leukemia.⁴ Obesity may also increase adverse effects due to chemotherapy as seen in the subtype of AML, acute promyelocytic leukemia (APL) as there are reports of severe cardiotoxicity with anthracycline-containing regimens requiring cardiac transplantation as a result of treatment in obese patients.¹⁰ Also, in pediatric patients with AML, underweight (BMI <11th percentile) and overweight (BMI >94th percentile) patients had a inferior survival than their counterparts.¹² The impact of obesity on the outcome of adults with newly diagnosed AML undergoing conventional induction chemotherapy has only recently been described by Medeiros and colleagues (manuscript submitted for publication) which showed that overweight and obese patients had a trend toward lower CR rates and more resistant disease.¹⁷

Our study suggests that empiric dose adjustment on the basis of obesity alone does not appear to affect outcomes or change toxicity significantly. It is interesting to note that obese subjects who did not receive an empiric dose reduction had a higher CR rate (12/14; 85.7%) compared to both those obese patients who received an empiric dose reduction (4/6; 66.7%) and non-obese patients (29/42; 69%).

This study evaluated the experience of a single, large, academic medical center and analyzed the association between increased percentage of ideal body weight (obesity) and outcomes of patients with newly diagnosed AML receiving their first induction chemotherapy. Similar to the general population, one-third of our study patients were obese. However, it is important to note that our definition is based upon percentage of IBW ($\geq 130\%$ IBW) rather than BMI. The overall number of patients classified as obese would have been reduced, though similar, had we chosen to utilize BMI to define obesity. Our alternative definition of obesity was chosen as it has been shown to be the most commonly utilized cutoff to determine dose-adjustments for chemotherapy in obese patients.¹⁴ In our study, obesity was not associated with a difference in CR rate, presence of MRD, delayed platelet recovery at 30 days, or delayed neutrophil recovery at 30 days.

The reason these data differs from that previously described from prior results described in children and adolescents with AML where extreme BMIs (underweight and overweight) predicted inferior survival, are not entirely clear. However, the definition of overweight/obese differed from our investigation. While we utilized an IBW $\geq 130\%$ of predicted IBW as our cutoff for obesity, Lange et al used the Centers for Disease Control (CDC) and

Prevention 2000 Growth Charts, where the normal weight was defined as a BMI between the 11th and 94th percentile. This difference in classification led to a disproportionately higher number of adults designated as overweight/obese (35% vs. 14.8%).¹⁹ Additionally, though overweight pediatric patients had increased treatment related mortality each BMI group had similar rates of complete remission between the various groups. Our study showed a non-significant trend toward improved rates of CR in our obese patients, particularly in those patients who did not receive empiric dose reductions for their therapy. In the end, the inherent inferior survival for adult AML patients may have lessened the impact of obesity on the outcome of these patients compared to pediatric AML patients. Our results are similar to those in most adult cancers, including leukemia, in which overweight/obese patients have excess cancer-related deaths rather than death from treatment related toxicities.²⁰

We acknowledge that there are several limitations to this study. This is a retrospective, unplanned analysis of an ultimately small population of patients with newly diagnosed AML receiving induction chemotherapy with 7 + 3. Although there was considerable variation in empiric dose adjustment, it seems the most common approach at our institution is to calculate an adjusted body surface area (BSA) based upon an adjusted body weight calculation. This is consistent with prior studies.¹⁴ At baseline the characteristics of our obese and non-obese populations were well-matched other than for gender. There were non-significant differences in cytogenetics and other prognostic factors. However, we addressed those differences through our multivariate analysis, which included the differing prognostic factors. It appears that obesity was not negatively associated with treatment outcomes or toxicity with induction chemotherapy for newly diagnosed AML. In most cases, obesity alone does not warrant empiric dose reductions. A larger, prospective randomized trial of empiric dose adjustment versus dosing on actual body weight and BSA would be required to confirm these results, though it may prove unfeasible to prospectively investigate this issue as most oncology practitioners dose with curative intent. Thus, it would be difficult to ethically randomize a patient to automatically receive a lower dose of chemotherapy.

Basic pharmacokinetic and pharmacodynamic studies of chemotherapeutic drug disposition in obese patients would provide a rational basis for dosing. However, until a randomized trial comparing dosing on actual versus adjusted body weight is conducted in obese patients it remains impossible to know whether doses of chemotherapy should be reduced. Dose reduction is likely to lead to increased relapse. It has been suggested elsewhere that relapse is the lesser of two evils when compared to increased toxicity.⁶ However, our data would suggest it is also possible that empiric dose reduction in this population has no effect on toxic mortality with the possible deleterious effect of increasing relapse.

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IBW = Ideal body weight:
Males: $IBW = 50 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet}$
Females: $IBW = 45.5 \text{ kg} + 2.3 \text{ kg for each inch over 5 feet}$

AjBW = adjusted body weight:
 $AjBW = IBW + 0.4(ABW - IBW)$

Figure 1. Ideal body weight calculations

Figure 2. Complete remission rates: obese vs. non-obese

Figure 3. Effect of cytogenetics on platelet and neutrophil recovery at 30 days

Table 1
Baseline Patient Characteristics

	Obese (≥ 130% IBW)	Non-obese	All subjects
• Age (yrs) (mean+/- SD)	55.4 ± 14	54 ± 10.97	54.5 ± 12
• % IBW (mean+/- SD)	162.3 ± 36.4	111.7 ± 11.3	128.6 ± 33
• Wt (kg) (mean+/- SD)	96.9 ± 31.9	74.1 ± 12.2	81.7 ± 23.3
Gender – N (%)	3 (14.3)	30 (71.4)	33 (52)
• Male	18 (85.7)	12 (28.6)	30 (48)
• Female			
Cytogenetics – N (%)	6 (28.6)	5 (11.9)	11 (17.5)
• Favorable	10 (47.6)	27 (64.3)	37 (58.7)
• Intermediate	5 (23.8)	8 (19.1)	13 (20.6)
• Unfavorable	0 (0)	2 (4.8)	2 (3.2)
• Unknown			
FLT3-ITD – N (%)	2 (9.5)	5 (11.9)	7 (11.1)
• Yes	5 (23.8)	17 (40.5)	22 (34.9)
• No	14 (66.7)	20 (47.6)	34 (54)
• Unknown			
NPM-1 – N (%)	2 (9.5)	7 (16.7)	9 (14.3)
• Yes	6 (28.6)	14 (33.3)	20 (31.7)
• No	13 (61.9)	21 (50)	34 (54)
• Unknown			
TOTAL – N (%)	21 (33)	42 (67)	63 (100)

Table 2
Characteristics of obese subjects

	Dose adjustment for obesity	No dose adjustment
• Age (yrs)	46.17 ± 17.5	59.1 ± 10.9
• % IBW	209.18 ± 34.39	143.6 ± 12.5
• BMI	45.5 ± 6.61	29.8 ± 2.7
• Male	2 (33.3)	1 (6.7)
• Female	4 (66.7)	14 (93.3)
Cytogenetics (%)	2(33.3)	4 (26.7)
• Favorable	3 (50)	7 (73.3)
• Intermediate	1 (16.7)	4 (26.7)
• Unfavorable		
FLT3-ITD (%)	1 (16.7)	1 (6.7)
• Yes	1 (16.7)	4 (26.7)
• No	4 (66.7)	10 (66.7)
• Unknown		
NPM-1 (%)	0(0)	2 (13.3)
• Yes	3 (50)	3 (20)
• No	3 (50)	10 (66.7)
• Unknown		
TOTAL (%)	6 (28.6)	15 (71.4)

Table 3
Univariate associations with CR (logistic regression)

	OR	P value
Obesity	1.14	0.26
Previous malignancy	0.89	0.34
FLT3	1.14	0.50
NPM-1	1.03	0.88
Gender	1.06	0.61
Karyotype	--	0.15*

*
Fisher's exact test