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Is obesity a prognostic factor for acute myeloid leukemia outcome?

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Abstract

Obesity adversely affects outcome in pediatric acute lymphocytic leukemia and acute myeloid leukemia (AML). We asked if obesity, measured by body mass index (BMI), affected outcome in 329 adult AML patients treated with high-dose cytarabine and idarubicin-containing regimens administered according to actual body weight. Age \geq 60, unfavorable karyotype, secondary AML, and positive smoking status had adverse impact on overall survival in a multivariate analysis, while BMI did not. We conclude that high BMI should not be a barrier to administer high-dose cytarabine-containing regimens for AML induction.

Keywords

Acute myeloid leukemia; Obesity; Body mass index; Outcome

Introduction

The prevalence of obesity has increased substantially over the past few decades and has more than doubled in adults in the USA [1]. Furthermore, obesity is a known risk factor for adult hematological malignancies [2]. Chemotherapy dosages for obese patients are often empirically reduced on the basis of ideal body weight because of concerns about excessive toxicity; however, dose reductions may compromise treatment outcomes [3, 4]. There is a paucity of information on the influence of body mass index (BMI) on the toxicity of intensive chemotherapy in adult AML and on progression-free survival (PFS) and overall survival (OS) following intensive chemotherapy [5, 6]. We compared toxicity data and survival outcomes across three BMI groups [normal (NL), overweight (OW), and obese (OB)], in 329 adults with AML, treated with similar AML induction chemotherapy administered by actual weights, to find out if obesity is a prognostic factor in AML.

Patients and methods

We queried the leukemia database for patients treated with high-dose cytarabine and idarubicin-containing regimens at the Roswell Park Cancer Institute (RPCI) between June 1990 and December 2008. Three hundred twenty-nine AML (except acute promyelocytic leukemia) patients eligible for high-dose cytarabine and idarubicin-containing regimens were found. The following patient data were scored: age, gender, weight, height, karyotype, smoking history, disease presentation (de novo vs. secondary), time of relapse, and allogeneic transplant. Patients' heights and weights were recorded at the time of induction chemotherapy. BMI was calculated using the World Health Organization (WHO) classification definition [7] and was categorized as follows: NL as BMI < 25 kg/m², OW as BMI between 25.0 and 29.9 kg/m², and OB as BMI ≥ 30.0 kg/m². In this population, only one patient (18.48 kg/m²) was classified as underweight according to the WHO definition (BMI < 18.5) and was therefore included in NL BMI category. The RPCI Scientific Review Committee and the Institutional Review Board approved the study.

Treatment

Induction chemotherapy consisted of high-dose cytarabine [3 g/m² (1.5 g/m² for age < 50) every 12 h×12 doses] and idarubicin (12 mg/m²×3 doses) based on actual body weight. Sixty-one of 329 patients received priming with arsenic trioxide (0.15 to 0.65 mg/kg) prior to high-dose cytarabine and idarubicin on a phase I clinical trial. Consolidation therapy varied over time. All patients had adequate renal, hepatic, and cardiac function prior to treatment initiation. Of note, 34 patients underwent allogeneic hematopoietic stem cell transplantation during first remission.

Statistical analyses

Response criteria were standard [8]. PFS was defined as time from diagnosis until time of relapse. OS was defined as time from diagnosis until time of last follow-up or death.

Univariate analyses

Descriptive statistics and chi-square tests were used to explore associations between body mass index (BMI) and other characteristics of interest. The log rank (Mantel–Cox) test within the Kaplan–Meier (KM) analysis was used to assess statistically significant differences in mean PFS and OS (in months) according to various participant characteristics. All analyses were stratified by participant BMI at diagnosis (NL, OW, and OB).

Pulmonary and cardiac toxicities, infection, and multi-organ failure toxicities were obtained from medical records and were categorized according to the common terminology criteria for adverse events version 3. Furthermore, patients were categorized as having no toxicity or at least mild toxicity in any of the preceding areas. Differences in toxicity levels were assessed using chi-square analysis.

Multivariable analyses

Cox proportional hazard modeling was used to assess prognostic factors of OS and was limited to the 267 patients for whom complete data for all variables in the model were available. Tests for interactions between variables of interest and groups were performed using Cox proportional hazard modeling for both PFS and OS outcomes. Data were censored at the time of allogeneic transplantation. Models of PFS and OS were adjusted for: age (<60 years vs. ≥60 years), gender (female, male), AML presentation (de novo vs. secondary), WBC count at diagnosis (<100×10⁹/L vs. ≥100×10⁹/L), smoking history (never, previous smoker, current smoker), treatment decade (1990–1999 vs. 2000–2008), and karyotype [9] (intermediate, unfavorable, favorable, and unknown). OS was analyzed among 267 patients, including 208 events and 59 censors; PFS was analyzed among 181 patients and included 130 events and 51 censors. Survival curves stratified by BMI at diagnosis were obtained from Cox proportional hazard models after simultaneous adjustment for the covariates listed previously by plotting at the mean of each covariate. All significance testing was based upon a *p* value of <0.05. Analyses were completed using SPSS version 14.0.

Results

There were 188 (57%) males and 141 (43%) females (median age 57 years, range 18–85). The median follow-up was 12.9 months (range<1–195). A total of 34 patients (10.3%) underwent allogeneic transplantation. Patients' BMIs ranged from 18.48 to 60.61 kg/m². Overall, approximately 16% of patients reached 5 years OS. BMI was similar among patients who did or did not proceed to transplantation. Other characteristics are shown in Table 1. There were significantly less smokers among the NL BMI patients ($P=0.023$) and more males among the OW BMI patients ($P=0.006$). No other differences were noted.

As shown in Table 2, there were significantly less ($P=0.014$) pulmonary complications for OW patients compared to NL or OB patients with regards to grade one pulmonary toxicities. However, no other statistically significant differences were discovered in the other (cardiac and infectious) toxicities among the different BMI groups. Pairwise comparisons found statistically significant differences in reporting pulmonary complications for both NL patients and OB patients compared to OW patients (NL vs. OW: $p=0.023$; OW vs. OB: $p=0.010$, not shown). However, there were no statistically significant differences in pulmonary toxicity between NL and OB patients ($p=0.782$), and no differences were found for either cardiac complications or infection between BMI subgroups. Overall, day 30 mortality was 5.7% for NL, 6.7% for OW, and 7.7% for OB patients and was not statistically different ($p=0.840$). Similarly, no statistically significant differences in 60-day mortality were observed by BMI category ($p=0.277$).

There was no statistically significant difference in OS for NL (36.5 months), OW (49.5 months), or OB patients (41.0 months) ($P=0.471$) based on univariate KM analysis (Table 3). Patients who received arsenic trioxide did not show difference in PFS or OS in Cox proportional model when compared to patients who did not receive arsenic trioxide. However, statistically significant differences in OS were observed for smoking status, age, karyotype, AML presentation, and treatment decade based on univariate analysis. Similarly, no significant differences in PFS were observed between BMI strata (Table 3); PFS for NL, OW, and OB were 37.6 vs. 51.9 vs. 55.4 months, respectively, ($P=0.247$) based on KM analysis. Additional analysis was performed excluding 34 patients who underwent allogeneic transplantation ($n=295$). No statistically significant differences in OS and PFS were noted between BMI subgroups (Fig. 1a and 1b) When patients were separated by decade of diagnosis, 213 patients (64.7%) were treated between 1990 and 2000, and 116 patients (35.3%) were treated after 2000. The mean OS in the 1990s was 35.3 months (95% CI: 27.4 to 43.2), compared to 41.9 months (95% CI: 34.0 to 49.9) in the 2000s ($P<0.01$).

In multivariate analysis, age 60 ($p=0.004$), unfavorable karyotypes ($p<0.001$), WBC count $100\times 10^9/L$ ($p=0.018$), secondary presentation ($p=0.047$), and smoking history (former: $p=0.001$; current: $p=0.048$) had adverse impact on OS. There were no statistically significant differences in OS for either OW patients (HR=0.88, 95% CI: 0.62–1.23, $p=0.446$) or OB patients (HR=1.04, 95% CI: 0.73–1.46, $p=0.845$) compared to NL patients. Similarly, no statistically significant differences in PFS were observed for either OW patients (HR=0.89, 95% CI: 0.58–1.36, $p=0.582$) or OB patients (HR=0.78, 95% CI: 0.50–1.23, $p=0.284$) in a multivariate analysis. However, a positive smoking history (former:

$p=0.004$) and unfavorable karyotype ($p=0.002$) remained detrimental to PFS. Diagnosis after 2000 was associated with longer PFS (HR=0.60, 95% CI: 0.38–0.94, $p=0.026$) but did not affect OS (HR=0.78, 95% CI: 0.55–1.12, $p=0.179$). In the multivariate analysis, no interactions between BMI and various patient characteristics were observed on either PFS or OS (Table 4).

Discussion

Obesity has been associated with an increased risk of developing adult AML, but no survival data have been systematically studied [1, 10–12]. Establishing an association between obesity and outcomes could have significant implications for AML management [13]. We observed no association between BMI and outcome in adults with AML. However, we did see a trend toward improved survival for OW young (18–39 year old) populations ($P=0.07$). This may represent the limitations of BMI as a predictive tool since many AML patients will likely be in the OW group [14].

Specifically, BMI makes no distinction between muscles versus fat mass, and therefore, muscular individuals can be categorized in a higher BMI status. Other methods to assess obesity status are waist circumference [16–18], neck circumference [19, 20], and hip-to-waist ratio [21]. All have been used to predict outcome. For example, a 20% increase in the risk of colon cancer recurrence or mortality was observed for every 10 cm increase in waist circumference [18]. This may represent improved classification complimentary to the BMI that is in current use. Furthermore, sensitivity analyses using an age- and gender-weighted BMI classification tool based on NHANES-1 classifications were set forth by Must et al [15] but were not widely adopted.

Our results are in contrast to those observed in pediatric AML. Specifically, a retrospective pediatric study showed poor outcome in obese and underweight children treated on Children's Cancer Group-2961 (CCG-2961) [5]. Both underweight and overweight children with AML had increased treatment toxicities and decreased OS. However, this study utilized a pediatric scale, overweight (>95th percentile) or underweight (<1.0 percentile), and not the BMI WHO classification, which may explain the discrepancy between our report and CCG-2961. Furthermore, obesity is related to incidence, complications, and prognosis in acute promyelocytic leukemia [10, 22–24], regardless of age. The reason for these discrepancies is not clear.

However, our results are similar to a large retrospective study in the transplant setting of AML patients [25]. In that study encompassing 4,215 patients, BMI was not an adverse prognostic indicator for outcome, regardless of donor source.

Cardiac and pulmonary complications in obese populations have been extensively studied, and obesity's negative impact was clearly documented in patients with non-malignant diseases [26, 27]. Infectious complications can be increased due to decreased mobility, and glucose intolerance due to obesity. In our study, there was a statistical difference in pulmonary complications between OW vs. OB and OW vs. NL populations. However, this difference did not appear to be a consistent finding throughout different grades of pulmonary

toxicities in the different BMI categories. Of note, we detected a trend toward OS advantage in the young (18–39 years old) OW population, which may have been due to less pulmonary toxicity in this group.

We observed that patients diagnosed and treated in the 1990s had a significantly inferior OS compared to >2000s. When stratified by BMI status, OS was significantly longer in the NL and OB groups treated after 2000 but, interestingly, not in the OW group. We suspect that the survival benefits most likely represent improvements in supportive care and possibly allogeneic stem cell transplantation methods. This progressive chronologic survival improvement benefit was seen previously in a large AML population study in Sweden where all ages, except patients older than 80 years, had survival benefits with progressive chronologic time points [28].

A major caveat of this study is the sample size, compared to studies conducted in stem cell transplantation and pediatric AML. However, AML is a rare disease, and this sample size was sufficient to detect differences in other well-accepted AML prognostic factors such as age, WBC count, karyotype, etc., suggesting that if indeed BMI had a role, we should have been able to detect it. Another caveat of this study is its retrospective design and the need to collect data from physician notes within each patient's medical chart.

Interestingly, patients who were former smokers had worse survival outcomes compared to current smokers. A possible explanation for this phenomenon is that patients who quit smoking did so because of significant deterioration of their health prior to AML diagnosis such as pulmonary complications. One of the limitations of the smoking data is the lack of temporality in assessing time since smoking cessation as the current data only assessed smoking status at diagnosis. Therefore, it is possible that the “former smokers” continued smoking until just prior to diagnosis or current smokers quit just after diagnosis with AML. Although this limitation of our data is likely to result in misclassification, smoking status was not the main exposure of interest studied in this manuscript.

In summary, obesity has been shown to adversely affect outcome in pediatric AML [5] and acute promyelocytic leukemia [39] but not in adult AML patients, based on our results. Therefore, we conclude that BMI is not a poor prognostic factor in AML and high BMI should not be a barrier for intensive induction chemotherapy.

Acknowledgments

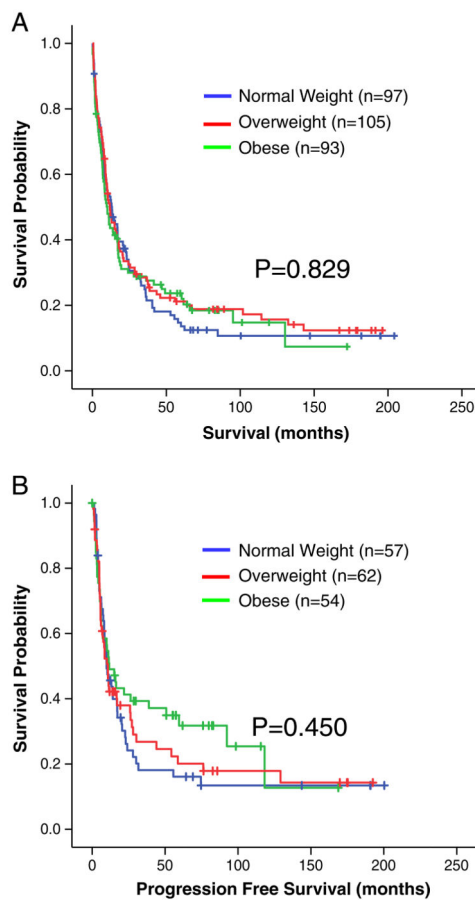
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**Fig. 1.**

a Curves based on Kaplan-Meier analyses assessing differences in overall survival by BMI status at diagnosis, excluding respondents who underwent allogeneic transplantation.

Normal weight: $n=97$ ($n=14$ censored); Overweight: $n=105$ ($n=18$ censored); Obese: $n=93$ ($n=19$ censored). The + sign reflects censored patients.

b Curves based on Kaplan-Meier analyses assessing differences in progression free survival by BMI status at diagnosis, excluding respondents who underwent allogeneic transplantation.

Normal weight: $n=57$ ($n=11$ censored); Overweight: $n=62$ ($n=15$ censored); Obese: $n=54$ ($n=17$ censored). The + sign reflects censored patients

Selected characteristics of the total study cohort and stratified by participant BMI status (normal vs. overweight vs. obese)

Table 1

	Total		Normal n=106 BMI<25.0		Overweight n=119 BMI 25.0–29.9		Obese n=104 BMI 30.0		p value
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
BMI									NA
Normal	106	32.2%							
Overweight	119	36.2%	NA	NA	NA	NA	NA	NA	
Obese	104	31.6%							
Smoking (n=281)									0.023
Never	101	35.9%	22	25.3%	40	40.0%	39	41.5%	
Previous	118	42.0%	37	42.5%	39	39.0%	42	44.7%	
Current	62	22.1%	28	32.2%	21	21.0%	13	13.8%	
Gender									0.006
Female	141	42.9%	46	43.4%	39	32.8%	56	53.8%	
Male	188	57.1%	60	56.6%	80	67.2%	48	46.2%	
Age									0.323
<60 years	178	54.1%	57	53.8%	59	49.6%	62	59.6%	
60 years	151	45.9%	49	46.2%	60	50.4%	42	40.4%	
AML presentation									0.119
De novo	229	69.6%	68	64.2%	81	68.1%	80	76.9%	
Secondary	100	30.4%	38	35.8%	38	31.9%	24	23.1%	
WBC count									0.811
<100×10 ⁹ /L	296	90.0%	97	91.5%	106	89.1%	93	89.4%	
100×10 ⁹ /L	33	10.0%	9	8.5%	13	10.9%	11	10.6%	
Karyotype (n=315)									0.585
Favorable	25	7.9%	5	4.9%	10	8.8%	10	10.0%	
Intermediate	144	45.7%	47	46.1%	56	49.6%	41	41.0%	
Unfavorable	114	36.2%	41	40.2%	37	32.7%	36	36.0%	
Unknown	32	10.2%	9	8.8%	10	8.8%	13	13.0%	
Mortality									0.277
Alive	63	19.1%	15	14.2%	25	21.0%	23	22.1%	

	Normal <i>n</i> =106 BMI <25.0		Overweight <i>n</i> =119 BMI 25.0-29.9		Obese <i>n</i> =104 BMI ≥30.0		<i>p</i> value		
	Number	Percent	Number	Percent	Number	Percent			
Total	266	80.9%	91	85.8%	94	79.0%	81	77.9%	
Decade of treatment									0.066
1990-1999	213	64.7%	74	69.8%	81	68.1%	58	55.8%	
2000-2008	116	35.3%	32	30.2%	38	31.9%	46	44.2%	
5-year survival									0.346
No	277	84.2%	93	87.7%	96	80.7%	88	84.6%	
Yes	52	15.8%	13	12.3%	23	19.3%	16	15.4%	

P value based on chi-square analysis, comparing BMI categories. Boldface *P* values represent chi-square analyses that are statistically significant at *p*<0.05 level

AML acute myeloid leukemia, WBC white blood cell

Table 2
 Frequency of reporting pulmonary toxicity, cardiac toxicity, or infectious complications (none vs. any) within 30 days of starting treatment by BMI status (normal: BMI<25.0; overweight: BMI 25.0–29.9; obese: BMI 30.0)

Toxicity	Overall		Normal		Overweight		Obese		p value
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Pulmonary									
None	172	52.4%	50	47.6%	75	63.0%	47	45.2%	0.014
Any ^a	156	47.6%	55	52.4%	44	37.0%	57	54.8%	
Cardiac									
None	176	53.7%	54	51.4%	69	58.0%	53	51.0%	0.494
Any	152	46.3%	51	48.6%	50	42.0%	51	49.0%	
Infection									
None	119	36.3%	41	39.0%	43	36.1%	35	33.7%	0.719
Any	209	63.7%	64	61.0%	76	63.9%	69	66.3%	

p value based on chi-square analysis comparing toxicities (none vs. any) of patients with differing BMI categories

^a Patient who suffered mild, moderate, severe, life-threatening, or death within 30 days of starting treatment were categorized as having “any” toxicity

Table 3
Mean overall survival and progression-free survival for various characteristics based on Kaplan–Meier analysis

	Overall survival (n=329)			Progression-free survival (n=207)			p value
	Number of individuals	Number of events	Mean (95% CI)	Number of individuals	Number of events	Mean (95% CI)	
BMI							
Normal	106	91	36.5 (24.6–48.4)	66	54	37.6 (21.2–54.0)	0.25
Overweight	119	94	49.5 (36.5–62.6)	76	54	51.9 (34.0–69.7)	
Obese	104	81	41.0 (28.8–53.2)	65	44	55.4 (37.6–73.3)	
Smoking status							
Never	101	71	61.2 (45.6–76.8)	66	42	65.3 (45.1–85.5)	0.02
Former	118	106	29.2 (20.6–37.7)	73	62	33.8 (20.9–46.1)	
Current	62	45	53.1 (32.9–73.3)	45	29	58.0 (31.8–84.3)	
Age							
<60 years	178	119	69.0 (55.7–82.3)	126	75	75.0 (57.9–92.1)	<0.01
60 years	151	147	20.8 (15.1–26.5)	81	77	22.9 (14.5–31.2)	
Sex							
Female	141	107	53.0 (39.9–66.2)	92	62	63.6 (43.5–79.7)	0.10
Male	188	159	37.9 (29.0–46.9)	115	90	41.8 (28.9–54.7)	
Cytogenetics							
Intermediate	144	112	51.4 (39.4–63.7)	103	77	51.8 (36.4–67.2)	<0.01
Unfavorable	114	101	27.8 (17.3–38.3)	62	51	32.7 (16.7–48.8)	
Favorable	25	10	124.2 (90.9–157.5)	22	7	117.8 (76.2–159.5)	
Unknown	32	29	25.6 (14.2–37.0)	17	14	25.3 (13.5–37.0)	
WBC count							
<100×10 ⁹ /L	296	240	44.7 (36.6–52.8)	186	138	50.0 (38.7–61.4)	0.61
100×10 ⁹ /L	33	26	37.8 (17.3–58.2)	21	14	52.7 (23.3–82.1)	
AML presentation							
De novo	229	147	54.3 (44.1–64.5)	147	99	57.2 (43.6–70.9)	<0.01
Secondary	100	75	21.8 (13.1–30.5)	37	34	25.5 (9.9–41.1)	
Treatment							
1990–1999	213	193	35.3 (27.4–43.2)	129	111	38.8 (27.6–50.0)	<0.01

		Overall survival (n=329)				Progression-free survival (n=207)			
	2000–2008	Number of individuals	Number of events	Mean (95% CI)	p value	Number of individuals	Number of events	Mean (95% CI)	p value
		116	73	41.9 (34.0–49.9)		78	41	46.7 (36.4–57.1)	

Mean survival and 95% CI were calculated from Kaplan–Meier analyses of overall survival time in months; *p* values based on log rank (Mantel–Cox) test of equality between different factor levels of each covariate. Boldface entries represent *p* values significant at *P*<0.05

CI confidence interval, *WBC* white blood cell count at diagnosis, *AML* acute myeloid leukemia

Multivariate analysis for OS ($n=234$) and progression-free survival ($n=148$) by selected characteristics based on Cox proportional hazard modeling excluding 34 patients receiving an allogeneic transplant

Table 4

Characteristic	Overall survival			Progression-free survival		
	Number	HR (95% CI)	<i>p</i> value	Number	HR (95% CI)	<i>p</i> value
BMI						
Normal	75	1.00		46	1.00	
Overweight	80	0.94 (0.65–1.35)	0.733	55	0.95 (0.60–1.52)	0.830
Obese	79	1.16 (0.80–1.67)	0.442	47	0.85 (0.51–1.42)	0.532
Smoking status						
Never	83	1.00		50	1.00	
Former	101	1.56 (1.10–2.20)	0.012	62	1.72 (1.07–2.75)	0.024
Current	50	1.31 (0.84–2.05)	0.234	36	1.32 (0.72–2.43)	0.378
Gender						
Female	99	1.00		63	1.00	
Male	135	1.05 (0.77–1.45)	0.757	85	1.19 (0.77–1.84)	0.429
Age						
<60 years	126	1.00		85	1.00	
60 years	108	1.52 (1.05–2.21)	0.028	63	1.25 (0.77–2.02)	0.371
Presentation						
De novo	169	1.00		118	1.00	
Secondary	65	1.36 (0.97–1.89)	0.073	30	1.12 (0.69–1.81)	0.662
WBC count						
<100×10 ⁹ /L	210	1.00		134	1.00	
100×10 ⁹ /L	24	2.20 (1.37–3.55)	0.001	14	2.22 (1.15–4.30)	0.018
Karyotype						
Intermediate	105	1.00		74	1.00	
Unfavorable	86	2.01 (1.45–2.79)	<0.001	42	1.73 (1.10–2.73)	0.017
Favorable	23	0.41 (0.20–0.83)	0.014	20	0.32 (0.13–0.75)	0.009
Unknown	20	1.09 (0.64–1.87)	0.744	12	1.13 (0.55–2.32)	0.740
Decade of treatment						

Characteristic	Overall survival		Progression-free survival	
	Number	HR (95% CI)	Number	HR (95% CI)
1990–1999	144	1.00	93	1.00
2000–2008	90	0.73 (0.50–1.07)	55	0.53 (0.32–0.89)

Thirty four allogeneic transplant patients were excluded from the model. Gender, age, AML presentation, WBC count, karyotype, and smoking status were entered into the model concurrently to assess hazard ratio. *P* value based on Cox proportional hazard modeling after adjusting for all other covariates. Boldface entries represent statistically significant hazard ratios compared to referent group ($p < 0.05$)

AML acute myeloid leukemia, CI confidence interval, WBC white blood cell