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Effects of obesity on overall survival of adults with acute myeloid leukemia

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Abstract

Background: The role of obesity in prognosis of acute myeloid leukemia(AML) is debatable. Our retrospective study aimed to determine the effect of obesity on overall survival(OS) in AML.

Methods: AML patients diagnosed at University of Nebraska Medical Center were divided into 3-groups based on body mass index (BMI): normal(18.5-25kg/m^2) or underweight(<18.5kg/m^2); over-weight(25-30kg/m^2); and obese(≥30kg/m^2). Chi-square test, Kruskal-Wallis test, and ANOVA were used to examine the association of BMI with baseline characteristics. Mann-Whitney test was used for pairwise comparisons of hematopoietic cell transplant(HCT) comorbidity index. Bonferroni correction was used to adjust p-values. OS, defined as time from diagnosis to death from any cause, was determined by Kaplan-Meier method; comparisons of survival curves were done using log-rank test. Cox Regression was performed to detect the effect of BMI on OS.

Results: Of 314 patients, 38% were obese, 68% received intensive chemotherapy, and 30% underwent HCT. Patient characteristics for all BMI groups were similar except greater HCT comorbidity index in obese patients. Actual body weight was used to dose chemotherapy in 92% of obese patients. The rate of receipt of HCT in normal, overweight, and obese groups were 33%, 32%, and 25% respectively(p=0.6). One-year OS for normal/underweight, overweight and obese groups was 42%, 45%, and 39% respectively(p=0.31). On a multivariate analysis,

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Conflict of Interest

VB reports receiving consulting fees from Pfizer, CSL Behring, Agios, Incyte, Partner Therapeutics and Abbvie, and research funding from Incyte, Tolero Pharmaceuticals, Inc, and National Marrow Donor Program. KG reports receiving consulting fees from Pfizer, Novartis, and Shionogi, and has stock in Portola Pharmaceuticals. All other authors declare no conflict of interest.

obesity was associated with worse OS, as compared to normal weight(hazard ratio-0.6; 95% CI[0.4-0.9],p=0.03) but not overweight patients.

Conclusion: Obesity confers worse prognosis in AML. Differences in OS was not the result of differences in dose of chemotherapy or receipt of HCT.

MicroAbstract

We aimed to determine the effect of obesity on overall survival(OS) in acute myeloid leukemia(AML). Total 314 patients were included in the study; 38% were obese. Actual body weight was used to dose chemotherapy in 92% of obese patients. On a multivariate analysis, obesity, compared to normal weight, conferred worse OS. OS was similar in obese and overweight patients.

Keywords

Myeloid neoplasm; Body mass index; Prognosis; Hematopoietic cell transplant; Outcomes

Introduction

Obesity is an established risk factor for multiple cancers [1-5]. Higher incidence of hematological malignancies, including acute myeloid leukemia (AML), has been reported with obesity [1, 6-9]. In fact, studies have shown more than 50% increase in risk of AML in obese patients [6, 9, 10]. The pathophysiology is still unclear, but carcinogenesis in obesity may be secondary to metabolic dysregulation associated with obesity [11, 12]. Different hormones, cytokines, adiponectin, leptin, and other factors associated with adipose tissue may lead to proinflammatory and growth-promoting environment for cancer cells [13]. There is evidence of specific organ dependent interaction between adipose tissue and cancer cells through various other mediators, which increases the risk of cancer [13]. In leukemia, adipose tissue in bone marrow promotes growth, fulfills metabolic demands, and provides protective environment to leukemic cells [14, 15]. Adiponectin, a multimeric protein in adipose tissue, has been speculated to alter hematopoietic stem cell function and assist with leukemic hematopoiesis [16]. Leptins and insulin-like growth factor may be other relevant candidates, especially for myelogenous leukemia [17-19].

Obesity has also been recognized as an adverse prognostic factor in some cancers [15, 20-24] High body mass index may not be an independent prognostic factor, but a surrogate for other risk factors including comorbidities, performance status, and disease severity [25]. Adipose tissue has been reported to attract acute lymphoblastic leukemia cells, and protect them from chemotherapy, leading to a higher chance of relapse [15]. Studies have shown adverse impact of obesity in acute promyelocytic leukemia, independent of age, sex, performance status, race and ethnicity [12, 26]. Obesity has also been linked with poor outcomes in pediatric AML patients [27-29].

The role of obesity in prognosis of adult patients with AML has been debatable. It is important to explore the relation between obesity and AML, which may lead to recognition of factors with potential diagnostic and prognostic utility [12]. This can be crucial in development of drugs and improve outcomes with AML in obese adults. In this context, the

aim of our study was to determine the effect of obesity on overall survival (OS) of adults with AML.

Materials and Methods

We conducted a retrospective single center study at the University of Nebraska Medical Center (UNMC). All new cases of AML diagnosed or treated at UNMC between the years 2000 to 2016 were identified via a query of the electronic health record. Patients with APL were excluded. The study was approved by the institutional review board.

We used BMI cutoffs to examine outcome of AML in relation to obesity. Based on the World Health Organization classification of BMI, patients were divided into 3 groups: underweight (<18.5 kg/m^2) and normal weight (18.5-24.9 kg/m^2); over-weight (25-39.9 kg/m^2); and obese (≥30 kg/m^2). Only one patient was underweight and was included in the normal BMI group. Chemotherapy used was divided into intensive and low intensity groups. Intensive chemotherapy included standard dose cytarabine with anathracycline (7 +3), and high or intermediate dose cytarabine with or without other chemotherapeutic agents, and etoposide with mitoxantrone. Low intensity chemotherapy included hypomethylating agents (azacitidine or decitabine), clofarabine, low dose cytarabine, gemtuzumab ozogamicin, and sapacitabine.

Chi-square test, Kruskal-Wallis test, and ANOVA were used to examine the association between BMI and other patient characteristics. Mann-Whitney test was used for pairwise comparisons of hematopoietic cell transplant (HCT) co-morbidity index, and Bonferroni correction was used to adjust p-values. OS, defined as the time from diagnosis to death from any cause, was determined by the Kaplan-Meier method, and comparisons were done using the log-rank test. Cox Regression was performed to detect survival effect of BMI (as continuous variable). $P<0.05$ was considered statistically significant.

Results

A total of 314 patients were included in the study; 28% were normal weight, 34% were overweight, and 38% were obese (Table 1). Among all patients, 46% were female, 35% had adverse cytogenetics, 15% had FLT3-ITD mutation, and 35% had NPM1 mutation. A total of 68% of patients received intensive chemotherapy, and 30% underwent HCT. Baseline characteristics were similar in all 3 groups except HCT co-morbidity index. Comorbidities including hypertension, coronary artery disease, and total bilirubin level were different in 3 groups. HCT comorbidity index was 1.9 ± 2 for obese patients compared to 1.6 ± 2.1 for normal or underweight patients, and 1.7 ± 2 for overweight patients (p=0.04). Actual body weight was used to dose chemotherapy in 92% of obese patients. There was no significant difference in the proportion of patients receiving intensive and low intensity chemotherapy in 3 BMI groups.

Complete remission (CR) or CR with incomplete hematological response (CRi) was achieved in 39% of normal or underweight patients, 39% of overweight patients, and 37% of obese patients (0.6) (Table 2). The rate of receipt of HCT in normal, overweight, and obese groups were 33%, 32%, and 25% respectively (p=0.6). OS for normal, overweight and obese

groups at 1 year was 42% (95% confidence interval [CI], 31-52), 45% (95% CI, 35-54), and 39% (95% CI, 30-47) respectively (p=0.31). BMI, as a continuous variable, was not a significant risk factor for death (Hazard ratio [HR] 1.003, 95% CI 0.98-1.02) (Figure 1).

In a univariate analysis, OS was better for patients <60 years, those with KPS 90-100, no adverse cytogenetics, and HCT-CI <3, and those who underwent intensive chemotherapy and transplant (Table 3). In multivariate analysis, obesity was associated with worse OS than normal weight (HR 0.6; 95% CI [0.4-0.9], p=0.03) (Table 4). No difference was detected between obese and over-weight groups. OS was worse with age ≥60 years, adverse cytogenetics, HCT CI ≥3, and low intensity or no chemotherapy.

Discussion

In our single center retrospective study, patient characteristics for all BMI groups were similar except greater HCT comorbidity index in obese patients, and specific comorbidities including hypertension, coronary artery disease, and total bilirubin level. Chemotherapy was dosed based on actual body weight in >90% of all obese patients. On a multivariate analysis, after adjusting for other variables, we determined worse OS with obesity compared to normal weight. CR/CRi and receipt of HCT were similar in obese, overweight and normal weight groups. Although the exact reasons remain unclear, these facts suggest that worse OS with obesity may have been influenced by either increased relapse rates or increased deaths from comorbidities; however, the retrospective study design did not allow us to definitely determine the cause of deaths in our study population.

Prior studies have shown variable results regarding the association of BMI with OS. Crysandt et al. reported worse OS in obese younger patients with de novo AML [30]. However, there was a dose cap based on body surface area, and results were worse in obese patients, likely secondary to reduced dosing and higher relapse rate. Lange et al., in an analysis of pediatric AML patients in Children's Cancer Group 2961 trial, concluded that mortality and toxicity were higher in overweight and underweight patients compared to patients with normal BMI [29]. . However, pediatric and adult AML patients cannot always be compared because of differences in pharmacokinetics, drug regimen, and nutritional status.

A few studies have reported no association of obesity on OS of newly diagnosed AML patients [14, 26, 31, 32]. In an analysis of adult AML patients enrolled in the Southwest Oncology Group trials, 2/3rd of total patients were obese or overweight and received higher doses of induction chemotherapy than normal weight patients [31]. Obese patients had higher response rates and lower resistance to chemotherapy but similar OS and treatment-related death or toxicities. A retrospective study by Castillo et al. included AML patients enrolled in Cancer and Leukemia Group B trials [26]. Actual body weight was used for dose administration in patients and the final results showed no significant prognostic value of obesity.

Obesity has also been reported to have better OS than other BMI groups [25, 33]. One retrospective study reported decreased OS for normal weight patients compared to

overweight or obese patients [34]. All patients in the study received cytotoxic chemotherapy based on actual body weight without significant toxicities. The authors reasoned that the results might have been influenced by relatively worse survival in underweight patients, although, only 7% of patients in the group were underweight. In contrast to abovementioned analyses, our study contributes to the literature by demonstrating worse OS in obese patients with AML despite actual weight-based doses, no difference in rate of chemotherapy utilization, responses and receipt of HCT.

Exact mechanism relating obesity to prognosis in AML is unclear. Studies suggest that obesity should not preclude aggressive treatment in AML patients, and actual body weight should be used for chemotherapy dose calculations [35-38]. It can be argued that similar dose per m^2 of body surface area in relatively matched obese and non-obese patients may lead to similar response to chemotherapy, and subsequently, similar outcomes. American Society of Clinical Oncology recommends actual body weight-based, and not a fixed or limited dose, in obese patients [37]. Underdosing of obese patients with adjusted or reduced doses may compromise response rates and OS [37].

Obesity alters pharmacokinetics for many medications, including chemotherapeutic agents, although the exact mechanism is not well understood. It has been suggested that half-life of doxorubicin is increased in obese individuals because of increased fat solubility and reduced systemic clearance [39, 40]. It is possible that daunorubicin may have greater peak concentration with decreased clearance, leading to higher response rates in obese AML patients [41, 42]. In contrast, normal weight patients may have relative underdosing because of lesser fat stores. In addition, it is postulated that leptins are increased in obese patients leading to proliferation of AML blasts, and subsequent increased sensitization to cytotoxic therapy [31, 43, 44]. However, none of these reasonings have been verified, and the effect of obesity on OS still remains controversial.

Our study has some potential limitations including single-center retrospective design and heterogenous chemotherapy regimens. As with prior studies, BMI may not always reflect the distribution of visceral and subcutaneous fat and may be inaccurate in evaluating adiposity in extreme BMI groups [12]. Our sample size was relatively small to allow analysis of various AML subsets. The study may not have adequate power to detect statistically significant differences in the intensity of chemotherapy chosen for patients with high BMI. However, we compared important baseline characteristics for all BMI groups including comorbidities and compared response rates and the use of HCT among patients treated in a real-world practice.

Conclusion

Obesity is associated with worse OS in patients with AML. Further prospective studies should explore the relationship of obesity on AML outcomes and the underlying mechanism.

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Clinical practice points

- The role of obesity in prognosis of AML is unclear; existing literature report variable results. In most studies, obesity had no effect on OS of AML patients. Some studies reported worse prognosis with obesity, especially on patients who got lower doses based on adjustment for weight.
- We sought to analyze the effect of obesity on OS of adults with AML. Chemotherapy was dosed based on actual weight in >90% of patients. In multivariate analysis, obesity, as compared to normal weight, was associated with worse OS. OS was similar between obese and over-weight groups.
- The remission rate and receipt of HCT were similar regardless of weight.
- Metabolic dysregulations, including altered pharmacokinetics of chemotherapeutic agents, may play a crucial role in prognosis of obese patients with AML.

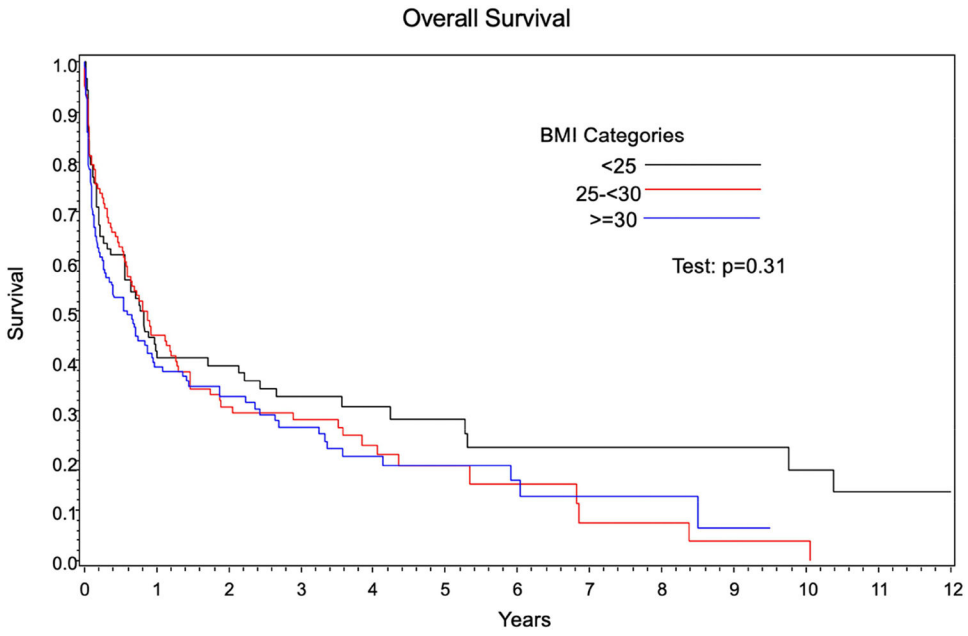

Figure 1:
Overall survival for acute myeloid leukemia based on body mass index

Table 1:

Patient characteristics

	BMI <25*	BMI 25-30	BMI ≥30	p-value
Total patients (n, %)	87 (27.7)	106 (33.8)	121 (38.5)	-
Age at diagnosis (years, mean ± SD)	59 ± 15	60 ± 14	59 ± 15	0.8
Sex (Female, %)	48 (55.2)	47 (44.3)	51 (42.5)	0.1
HCT co-morbidity index at diagnosis (mean ± SD)	1.6 ± 2.1	1.7 ± 2	1.9 ± 2	0.03
Comorbidities †				
• Coronary artery disease	3 (3.4)	9 (8.5)	16 (13.2)	0.04
• Hypertension	15 (17.2)	33 (31.1)	62 (51.2)	<0.0001
Total bilirubin >1 mg/dl †	19 (22.1)	6 (5.8)	27 (22.9)	0.0005
KPS at diagnosis	84 ± 14	86 ± 10	86 ± 12	0.7
WHO group at diagnosis (n, %)				0.9
• AML with recurrent genetic abnormalities	17 (21.2)	22 (22.2)	23 (21.9)	
• AML with myelodysplasia related features	21 (26.2)	27 (27.3)	28 (26.7)	
• Therapy related AML	7 (8.8)	6 (6.1)	10 (9.5)	
• AML, NOS	35 (43.8)	44 (44.4)	43 (41.9)	
Cytogenetic risk categories (n, %)				0.9
• Favorable	9 (11.1)	9 (8.6)	10 (9.4)	
• Intermediate	42 (51.9)	61 (58.5)	58 (54.7)	
• Adverse	30 (37)	35 (32.7)	38 (35.9)	
FLT3 ITD mutation positive (n,%)	13 (32.5)	19 (40.4)	14 (29.2)	0.5
NPM1 mutation positive (n,%)	13 (48.1)	11 (29.7)	11 (30.6)	0.2
Initial chemotherapy (n,%)				0.5
• Intensive	63 (72.4)	71 (67)	81 (66.9)	
• Low intensity	16 (18.4)	25 (23.6)	33 (27.3)	
• None	8 (9.2)	10 (9.4)	6 (5.8)	
Consolidation chemotherapy after remission (n, %)				0.2
• Intensive	40 (81.6)	40 (70.2)	45 (81.8)	
• Low intensity	0 (0)	7 (12.3)	2 (3.6)	
• None or unknown	8 (16.3)	9 (15.8)	7 (12.7)	

*One patient had BMI <18.5

†Only comorbidities significantly difference among BMI groups are included.

AML- Acute myeloid leukemia, BMI- Body mass index, CR- Complete remission CRi- Complete remission with incomplete hematological response, HCT- Hematopoietic cell transplant, KPS- Karnofsky performance scale, NOS- Not otherwise specified, SD- Standard deviation, WHO- World Health Organization

Table 2:

Outcome in acute myeloid leukemia patients based on body mass index

	BMI <25*	BMI 25-30	BMI ≥30	p-value
CR/CRi after initial chemotherapy (n,%)	34 (39.1)	41 (38.7)	45 (37.5)	0.6
HCT performed (n, %)	29 (33.3)	33 (32)	29 (24.8)	0.6
Cause of death (n, %)				0.5
• **AML**	37 (49.3)	58 (59.2)	60 (57.7)	
• **Treatment complications**	10 (13.3)	14 (14.3)	12 (11.5)	
• **Others**	1 (1.3)	2 (2)	5 (4.8)	
AML in remission at the time of death (n, %)	13 (15.5)	11 (10.9)	22 (19.5)	0.3

* One patient had BMI <18.5, AML- Acute myeloid leukemia, BMI- Body mass index, CR- Complete remission CRi- Complete remission with incomplete hematological response.

Table 3:

Univariate analysis of overall survival

	Hazard ratio	95% confidence limits	p-value
Age ≥60 vs <60	2.4	1.8-3.1	<0.0001
KPS 80 vs 90-100	1.5	1.2-2.1	0.0008
Favorable vs adverse cytogenetics	0.3	0.2-0.6	0.0004
Intermediate vs adverse cytogenetics	0.5	0.4-0.7	<0.0001
HCT comorbidity index ≥3 vs 0-2	1.4	1.1- 1.9	0.003
Low intensity vs intensive chemotherapy	3.3	2.4-4.5	<0.0001
No chemotherapy vs intensive chemotherapy	8.5	5.3-13.7	<0.0001
HCT- Yes vs No	0.3	0.2-0.4	<0.0001

HCT-Hematopoietic cell transplant, KPS- Karnofsky performance scale

Table 4:

Multivariate analysis of overall survival

	Hazard ratio	95% confidence limits	p-value
BMI <25 vs ≥30 *	0.6	0.4-0.9	0.03
BMI 25-30 vs ≥30	0.7	0.5-1.1	0.1
Age ≥60 vs <60	1.7	1.2-2.4	0.0005
KPS 80 vs 90-100	1	0.7-1.3	0.9
Favorable vs adverse cytogenetics	0.4	0.2-0.7	0.008
Intermediate vs adverse cytogenetics	0.5	0.3-0.6	<0.0001
HCT comorbidity index ≥3 vs 0-2	1.2	0.9-1.7	0.09
Low intensity vs intensive chemotherapy	2.3	1.6-3.4	<0.0001
No chemotherapy vs intensive chemotherapy	9.7	5.3-17.5	<0.0001

* One patient had BMI <18.5. BMI- Body mass index; HCT- Hematopoietic cell transplant; Karnofsky performance status