Impact of body-mass index on the outcome of adult patients with acute myeloid leukemia

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ABSTRACT

Background
Obesity increases the risk of treatment-related complications and reduces survival in children with acute myeloid leukemia. Little is known about the impact of obesity on the outcome of adult patients with acute myeloid leukemia.

Design and Methods
We compared the baseline characteristics and effect on treatment and survival in 1,974 previously untreated adult patients with acute myeloid leukemia undergoing treatment, according to international classification of body-mass index.

Results
The median body-mass index was 26.7 (15.5-61) and 63% of patients were overweight/obese. After adjustment for other confounders, such as age, gender, performance status, karyotype, white blood cell, platelet and peripheral blast counts, obese patients had better complete remission rates (P=0.0046), lower rates of resistant disease (P=0.038) but similar rates of survival and severe adverse events.

Conclusions
In the treatment of acute myeloid leukemia in adults, obesity was associated with increased response rates and no apparent increase in toxicity. Obesity should not, therefore, be a criterion for excluding patients from aggressive therapy.

Key words: body mass index, acute myeloid leukemia, outcome, adults.

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Introduction

Acute myeloid leukemia (AML) is a clonal hematopoietic disorder and the most common myeloid malignancy in adults.[1] Each year, approximately 13,000 individuals are diagnosed with AML in the United States with a median age at presentation of about 70 years. Given the expected shift in age structure the projected incidence of AML is expected to increase by approximately 50% by 2030.[2]

The prevalence of obesity has steadily increased in developed countries,[3,4] in which nearly two-thirds of adults are overweight (body-mass index [BMI] >25).[5] Obesity is associated with an increased risk of mortality from cardiovascular causes and malignancies.[3] Associations between increased BMI and leukemia and acute promyelocytic leukemia have been reported.[6,7] Reduced overall survival, due to higher rates of treatment-related toxicities, was noted in overweight children with AML.[8] As the effect of BMI at diagnosis in adult AML patients is unknown, we studied the prognostic impact of BMI on response, toxicity and survival in AML patients treated in studies conducted by the Southwest Oncology Group (SWOG).

Desgin and Methods

Patients

A total of 1,974 AML patients enrolled in one of ten consecutive SWOG studies were included.[11] Patients with acute promyelocytic leukemia were excluded. BMI at diagnosis was calculated as weight in kilograms divided by height in meters squared. Patients were stratified according to the World Health Organization (WHO) BMI classification into underweight (BMI <18.4), normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9) and obese (BMI >30). Obese patients were further divided into those with class I (BMI 30-34.9), class II (BMI 35-39.9) or class III (BMI >40) obesity. Centrally reviewed and approved cytogenetic data from diagnosis were stratified according to revised SWOG criteria.[9] Induction therapies were grouped into those: (i) with "standard" doses of cytarabine (≤200 mg/m^2 daily for 7 days) (n=814), (ii) with higher than "standard" doses of cytarabine (at least 1 g/m^2, per dose) (n=113), or (iii) without cytarabine (n=148). For patients achieving a complete remission, consolidation therapy varied based on the protocol design. Following SWOG chemotherapy dosing principles, actual body surface area was used to calculate treatment doses. For patients whose actual body weight exceeded by twice the ideal body weight (n=17), treatment was given at the discretion of the investigator. Only one patient received treatment according to ideal body weight. Seven patients with BMI greater than 61 kg/m^2 were excluded due to erroneous data entry. Grade 3 and 4 severe adverse events were included only if a possible, probable or definite relation to treatment could be established. All participating patients gave informed consent prior to enrollment into the studies. The studies were approved by ethics committees of all participating institutions and conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Complete remission was defined according to the Dohner criteria.[10] Induction death was defined as death within 28 days of initiating therapy. Patients were defined as having resistant disease when they were alive more than 28 days after initiating therapy but had never achieved complete remission or had relapsed within 1 year of achieving complete remission. Overall survival was measured from the date of entry into the study until death from any cause, with censoring at the date of last contact. Fisher's exact test was used to test associations between categorical variables. The Kruskal-Wallis test was used to determine associations between age and BMI classes. The Wilcoxon rank-sum test was used to compare the toxicity profile according to median BMI. The Kaplan-Meier method was used to estimate median overall survival.[11] Cox proportional hazards models were used to assess associations with overall survival.[12] Logistic regression models were used to assess associations with complete remission and resistant disease. BMI was measured both as a continuous numerical variable and as a categorical variable corresponding to the WHO classes in these models (Table 2). Only the data from the 1,080 patients with confirmed karyotype were included in the logistic regression analyses.

Results

Baseline characteristics of the patients

The median age of the patients was 57 years (range, 17-89 years). The median BMI was 26.7 (range, 15.5 to 61). Sixty-four percent of the patients were overweight and one quarter were obese. Table 1 presents the distribution of WHO BMI classes. No significant associations were noted between BMI class and karyotype (P=0.88). As previously shown, older age was associated with higher BMI; the underweight group had the youngest median age (50 years) while the overweight group had the oldest median age (59 years) (P=0.002). The incidence of obesity and the median BMI tended to increase over time: whereas patients enrolled during the 1980s (in trial S8600) had a median BMI of 24.5 (overweight/obese = 45%), those enrolled in the early 1990s (in trials S9031, S9126, S9333, and S9500) had a median BMI of 26.4 (overweight/obese

Table 1. Summary of the distribution of BMI groups according to cytogenetic risk group.[11]

Cytogenetic Risk (%)	BMI Groups (%)			
	Underweight (3)	Middleweight (34)	Overweight (38)	Obese (25)
Favorable (11)	3	35	33	30
Intermediate (47)	3	34	38	25
Unknown (9)	4	38	37	21
Adverse without MK (19)	3	35	40	21
Adverse with MK (14)	3	30	41	27

BMI: body mass index; MK: monosomal karyotype.

Table 2. Impact of BMI on complete remission rate, resistant disease rate, and overall survival for patients with AML from unadjusted logistic and Cox regression models including all patients (n = 1974).

BMI Groups	Outcomes								
	CR (%)	OR (95% CI)	P	RD (%)	OR (95% CI)	P	5-year OS%	HR (95% CI)	P
BMI[##]		1.02 (1.00, 1.03)	0.03		0.99 (0.97, 1.01)	0.24		0.997 (0.99, 1.006)	0.56
Underweight	49	0.88 (0.49–1/58)	0.66	60	0.81 (0.43–1.56)	0.53	19	0.996 (0.71, 1.40)	0.98
Normal Range	52	Ref	Ref	65	Ref	Ref	18	Ref	Ref
Overweight	53	1.03 (0.83–1.26)	0.81	65	1.00 (0.78–1.27)	0.98	19	0.998 (0.88, 1.13)	0.97
Obese									
Class I	55	1.11 (0.85–1.45)	0.44	64	0.94 (0.69–1.28)	0.69	19	1.01 (0.86, 1.18)	0.90
Class II	61	1.42 (0.94–2.14)	0.29	62	0.88 (0.55–1.40)	0.58	17	0.94 (0.74, 1.20)	0.60
Class III	60	1.40 (0.90–2.18)	0.14	55	0.67 (0.41–1.09)	0.11	26	0.81 (0.62, 1.08)	0.15

[##]BMI measured as a continuous variable; OR: odds ratio; HR: hazard ratio; CR: complete remission rate; RD: resistant disease rate; OS: overall survival; Normal range is the reference (Ref) category for both the CR and RD.

= 63%), and those enrolled more recently (in trials S9617, S9918, and S0106) had a median BMI of 27.7 (P<0.001) (overweight/obese = 69%, P<0.001).

Impact of body-mass index on response to therapy and survival

Table 2 demonstrates the impact of BMI on the rates of complete remission, induction death, resistant disease and overall survival. No significant differences in the rates of complete remission, resistant disease and 5-year overall survival were noted when AML patients were stratified into BMI groups. Increasing BMI, measured as a continuous variable, was associated with higher complete remission rates. When only patients with known karyotype were considered (n=1,080), increased BMI, as a continuous variable, was associated with higher complete remission rates and lower rates of resistant disease. Similar trends were noted in patients with class III obesity. The dose of cytarabine, when added as a variable to the regression models, did not affect responses and/or survival (*data not shown*). Additionally, there was no evidence that different BMI values had different associations with outcomes with different treatments.

Multivariate analysis of prognostic factors

Adjusting for age, gender, karyotype, performance status, white blood cell count, platelet count and peripheral blood blast count, class I obesity (P=0.021 and P=0.036) and class III obesity (P=0.029 and P=0.023) were associated with significantly higher complete remission rates and lower resistant disease rates (Table 3). Similar results were noted when BMI was measured as a continuous variable (complete remission rate, P=0.0046 and resistant disease rate, P=0.038). No association was noted between BMI and death during induction or survival.

Toxicity profile according to body-mass index

Overweight/obese patients received higher total doses of chemotherapy. However, no significant differences in toxicities were noted in these patients (Fisher's exact test P=0.46) nor were there differences in the median BMI in patients who did or did not have adverse events (P=0.66). Unadjusted and adjusted logistic regression analyses with adverse events as the outcome showed no significant association between toxicity and BMI.

Table 3. Adjusted logistic regression models for complete remission and resistant disease.

Prognostic factors	OR for CR	P	OR for RD	P
BMI (continuous)	1.03	0.004	0.97	0.01
BMI Groups (Normal-ref)				
Underweight	1.21	0.64	0.37	0.03
Overweight	1.23	0.20	0.81	0.31
Class I obese	1.40	0.10	0.60	0.04
Class II obese	1.39	0.34	1.14	0.75
Class III obese	2.38	0.02	0.33	0.004
Age	0.98	<0.001	1.02	<0.001
Gender				
Male (Female-ref)	1.00	0.98	0.80	0.19
Karyotype[11] (Favorable-ref)				
Intermediate	0.40	<0.001	1.60	0.06
Unknown	0.37	0.002	1.70	0.13
Unfavorable MK-	0.28	<0.001	2.70	<0.001
MK+ AML	0.12	<0.001	9.96	<0.001
Performance status	0.68	<0.001	1.43	0.002
White blood cell count	0.999	0.47	1.00	0.66
Platelets	1	0.87	1	0.67
Peripheral blasts	0.999	0.74	1.01	0.05

BMI: body mass index; CR: complete remission; OR: odds ratio; HR: hazard ratio; RD: refractory disease; WBC: white blood cell count; MK: monosomal karyotype. Logistic regression model adjusted for age, gender, performance status, white blood cell count, platelet count, and peripheral blood blast count.

Discussion

The epidemic of obesity has become a global health problem. Worldwide, 2.3 billion adults will be overweight and approximately one-third of these will be considered obese by 2015. Our study is the largest dataset to determine the impact of BMI on the outcome of adult AML patients undergoing induction chemotherapy. Two-thirds of the patients were overweight/obese and median BMI increased with age at diagnosis and over time. Also, in our cohort, increased BMI was associated with higher response rates and lower rates of resistance to chemotherapy, but had no impact on survival, treatment-related deaths or toxicities. These were surprising findings as obe-

sity is associated with an increased risk of diabetes and cardiovascular disease, which can increase toxicity in patients.[13]

Our results contrast with those reported in children and adolescents with AML, in whom extreme BMI values predicted inferior survival. There are several possible explanations for the contrasting results. First, the definitions of underweight and overweight were different. We used the WHO criteria[14] while Lange *et al.* used the Centers for Disease Control and Prevention 2000 Growth Charts.[15] Therefore, a higher proportion of adults were classified as obese (26% *versus* 15%) and more children/adolescents were classified as underweight (11% *versus* 3%).[8] Second, obese children had increased treatment-related mortality, but similar relapse risks.[8] In contrast, obese adult patients had increased response rates, with no increase in treatment-related deaths or toxicities. The reasons for these discrepancies are unclear and warrant further investigation.

The pharmacokinetic effects of obesity on daunorubicin metabolism are not well understood. Some studies have suggested that the half-life of doxorubicin is longer in obese subjects because of reduced systemic clearance and such subjects may, therefore, have greater exposure to the drug.[16] Other studies, however, suggest that dose reductions of anthracylines in obese patients may be associated with similar toxicities but worse outcomes.[17] It is possible that obese AML patients could have longer exposure to daunorubicin, translating into higher response rates. Two recent studies showed that daunorubicin dose intensification is associated with improved outcomes in AML, especially in younger patients.[18,19] The lack of a clear increase in toxicity in obese patients may reflect the insensitivity of current methods of measuring toxicity. Alternatively, leptins, which are increased with obesity, have been shown to increase the proliferation of AML blasts, which could sensitize these cells to cytotoxic agents.[20]

This study has clear limitations. This was a retrospective, unplanned analysis. Physicians may have been reluctant to enter obese patients with significant co-morbidities into these trials, leading to a bias in the selection of patients. We have no data on confounding factors, such as socioeconomic status. The methods for measuring toxicity were likely imprecise. Nonetheless, our results underscore the increasing prevalence of obesity in this population and demonstrate that obesity may be associated with increased response rates, and suggest that overweight patients should not be denied the potential benefits of aggressive therapy.

Authorship and Disclosures

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