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Letter to the Editor

Higher body mass index is associated with better survival in patients with myelodysplastic syndromes

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1. Introduction

Myelodysplastic syndromes (MDS) comprise a group of heterogeneous clonal hematopoietic stem cell disorders characterized by cytopenias(s), morphologic evidence of dysplasia in one or more hematopoietic cell lines, and ineffective hematopoiesis. Patients with MDS have a variable risk of progression to acute myeloid leukemia (AML). The pathophysiology of MDS is complex and involves abnormalities in the regulation of cellular proliferation, maturation, and interactions with the bone marrow microenvironment that result in heterogeneous outcomes. MDS generally arise *de novo* but also may arise after exposure to cytotoxic chemotherapy, radiation, smoking, and occupational chemicals such as benzene. Genetics and obesity also have been proposed as predisposing risk factors for MDS [1].

Obesity is a condition in which abnormal or excessive fat accumulation can lead to multiple health problems, such as increased risk of cardiovascular diseases, hypertension, and type 2 diabetes. Recent studies have linked obesity to an increased risk of colon, esophageal, pancreatic, and renal tumors [2,3], as well as endometrial, ovarian and breast cancers in post-menopausal women [4]. Various reports have also suggested associations between body size and risk of lymphohematopoietic malignancies including acute myeloid leukemia, lymphomas, myeloproliferative neoplasms and plasma cell myeloma [5–7]. However, the impact of obesity in the progression and survival of MDS patients is unclear. The aim of this study is to retrospectively evaluate and analyze the correlation of obesity with survival outcomes in MDS patients.

2. Methods

This study was approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center (UTMDACC) and was conducted in accordance with the Declaration of Helsinki. We searched the electronic medical records at UTMDACC for adult patients (older than 18 years) who were diagnosed MDS at our institution between January 1, 2006 and December 31, 2010, and for whom complete clinical information was available as well as bone marrow pathology, and cytogenetic and molecular data. Pathology reports of all patients were reviewed to confirm the diagnosis of MDS according to the 2008 WHO classification. Patients were stratified into risk groups according to International Prognostic Scoring System (IPSS). Patients who underwent stem cell transplant were excluded from this study due to substantial impact on patient survival. Enrolled patients were categorized into six weight groups based on their body mass index (BMI): underweight (BMI < 18.5), normal (BMI, 18.5–24.9), overweight (BMI, 25–29.9), obese-I (moderately obese; BMI, 30-34.9), obese-II (severely obese; BMI, 35–39.9), obese-III (very severely obese; BMI, 40.0 or higher), although the three obese groups were combined for most of the data analysis. Patient information was anonymized and de-identified prior to analysis.

Statistical analysis was performed using SPSS software from IBM (Armonk, NY). Categorical variables were analyzed using Pearson Chi-square, and continuous variables using Kruskal-Wallis rank sum tests. Overall survival (OS) was estimated using a reference time point, the date of initial MDS diagnosis until death from any cause or date of last follow-up. Progression-free survival (PFS) represented the duration between the initial MDS diagnosis and the progression into AML. Patient survival was plotted by the Kaplan-Meier method and differences were compared using the log rank test. Multivariate analysis was performed by Cox proportional regression model to examine the relationship between OS or PFS and patient characteristics. Differences between two groups were considered significant if p-values were < 0.05 in a two-tailed test.

3. Results and discussion

A total of 419 MDS patients, 257 men and 162 women, met the selection criteria and formed the study group. The clinicopathologic characteristics of patients in each weight group are summarized in Table 1. Compared to the general population of the United States (US) (http://www.win.niddk.nih.gov/statistics/), overweight and obese individuals were less prevalent in the group of MDS patients (P = 0.002). Other than a slight male predominance in the overweight and obese groups, (P = 0.031), there was no significant difference in age, diagnostic bone marrow blast count, blood hemoglobin level, absolute neutrophil count, platelet count, frequency of therapy-related MDS, or

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Table 1
Clinicopathologic characteristics of myelodysplastic syndromes (MDS) patients in each weight group.

	Underweight (N = 14)	*Normal (N = 148)*	*Overweight (N = 150)*	*Obese I, II, III (N = 107)*	*Total (N = 419)*	*P value*
Age, median (range), year	64.0 (22-79)	65.6 (19-88)	67.1 (31-91)	66.1 (33-87)	66.1 (19-91)	0.476
Female	78.6%	40.5%	31.3%	41.1%	38.7%	0.004
Height, mean (SD), cm	165.8 (7.75)	171.3 (9.71)	170.6 (8.89)	169.4 (9.91)	170.4 (9.45)	0.133
Weight, mean (SD), kg	46.8 (5.73)	65.8 (9.33)	79.9 (9.28)	99.9 (18.19)	78.9 (18.82)	< 0.001
BMI, mean (SD), kg/m^2	17.0 (0.95)	22.4 (1.72)	27.4 (1.33)	34.7 (5.19)	27.1 (5.91)	< 0.001
BM blast, median, %	9	7.5	6.5	7	7	0.474
Hemoglobin, median, g/dL	9.0	9.9	9.8	10.0	9.8	0.244
Absolute neutrophil, median, $10^3/\mu L$	0.8	1.1	1.3	1.5	1.3	0.185
Platelet, median, $10^3/\mu L$	79	84	88	88	87	0.97
Cytogenetic risk group						0.047
Favorable	35.7%	47.3%	56.7%	59.8%	53.5%	
Intermediate	7.1%	16.2%	17.3%	84.0%	14.3%	
Unfavorable	57.1%	36.5%	26.0%	31.8%	32.2%	
IPSS risk group						0.211
Low	7.1%	18.2%	30.0%	29.9%	25.1%	
INT-1	21.4%	27.7%	22.0%	18.7%	23.2%	
INT-2	50.0%	33.1%	32.7%	31.8%	33.2%	
High	21.4%	20.9%	15.3%	19.6%	18.6%	
Therapy-related MDS	28.6%	10.8%	16.7%	15.9%	14.8%	0.213
Mutations						
NRAS (n = 397)	8.3%	7.8%	6.1%	7.3%	7.1%	0.946
FLT3 (n = 416)	3.6%	4.4%	3.3%	1.5%	3.2%	0.303
NPM1 (n = 334)	0.0%	3.2%	3.2%	4.3%	3.3%	0.881

BMI, body mass index; BM, bone marrow; IPSS, International Prognostic Scoring System; INT, Intermediate.

frequency of common gene mutations among weight groups. Although apparently a higher percentage of IPSS low-risk patients were in the overweight and obese groups, the differences were not statistically significant. Furthermore, the significant differences in gender and cytogenetics were mainly seen within the underweight group, which were mostly women (78.6% vs 38.7% in overall cohort) with unfavorable cytogenetic results (57.1% vs 32.2% in overall cohort). Once the underweight group was excluded from the comparison, differences in these factors were not significant (P = 0.304 and 0.112, respectively). These findings suggest that obesity among MDS patients is less prevalent than is the prevalence among the general US population, and except underweight group, the clinicopathologic composite of MDS patients in different weight groups is similar.

We then assessed the impact of body mass on patient survival and disease progression in MDS. Our study cohort had a median follow up interval of 18 months, and showed significant differences in OS according to IPSS categories (P < 0.001; Fig.1A), confirming that the study cohort was representative of an MDS patient population. While differences in OS among all weight groups were not statistically significant (P = 0.206; Fig. 1B), the difference was significant when comparing combined overweight and obese groups with combined underweight and normal groups (Fig. 1C). It also appears that overweight and obese groups trended to better long-term survival. This observation was confirmed when comparing patients who survived with follow-up data for 12 months or longer after MDS diagnosis (N = 269; P = 0.016; Fig. 1D). Moreover, patients in the overweight and obese groups sustained a significant longer survival period without progressing into AML compared to those of normal weight (P = 0.001; Fig. 1E). Multivariate analysis indicated that higher BMI is a favorable factor for progression-free survival (PFS) independent of age, gender, IPSS score, hemoglobin or platelet counts (HR 0.496, 95% CI 0.326-0.755; P = 0.001; Table 2). These findings suggest that overweight and obese MDS patients are less likely to progress to AML and have an extended long-term survival.

Since this study cohort was from a single large academic medical center, our results may be subject to referral bias, as may be implied by the younger median age of patients (66.1 years) in this study compared with that of MDS patients in general (70 years). Extra-hematologic comorbidities, including obesity, are reported in MDS patients to affect the probability of survival [8]. Without data of different extra-hematologic comorbidities in our analysis of obesity might be a source of bias. Also, our results cannot establish a causal sequence between obesity and MDS because no control group included in this study. Nevertheless, this study is the first in the literature to correlate patient body mass with clinical outcomes in MDS with a longer period of follow-up. In addition, the lower prevalence of obesity in MDS patients in this study cohort compared with that of general US population implies that obesity may not be a common major cause of developing MDS.

The prevalence of obesity in the US increased during the last decades of the 20th century. The recent national health and nutrition examination survey indicates that overall about 68% of the US population was at the upper limit of BMI [9]. Various epidemiologic studies have shown correlation between obesity and cancer; however it was until Calle et al [10] conducted a large prospective study examining the role of obesity in increasing the risk of mortality from various tumors. Obesity has been associated with increased mortality secondary to cardiovascular diseases, stroke, diabetes mellitus, renal diseases and risk of developing cancer, noteworthy among the latter are hematopoietic malignancies. Many studies have reported a poor outcome in obese cancer patients. One potential explanation for inferior outcome in overweight or obese cancer patients might be related to the suboptimal dosage of chemotherapeutic drugs because of fear of treatment toxicity. Surgery as well as radiation therapy also can be technically more difficult than in normal weight patients and surgical recovery and outcomes have been reported to be worse among the obese patient population.

In contrast, our findings suggest that being overweight or obese tends to be a favorable survival factor in MDS patients. The explanations for this observation are unclear. One possibility is that therapy, calculated based on body weight, may be administered at higher dosage at the time of therapy as has been reported by others [11]. Other possible explanations could be lower risk factors at the time of MDS presentation or less cachexia in these patients. Interestingly, a recent study on a murine model revealed that obesity could increase survival in animals with MDS by retaining myeloid cells in the adipose tissue [12]. Increased adiposity was also found to be associated with a reduced risk of premenopausal breast cancer in a new large-scale study [13]. Altogether, these counterintuitive findings shed new light on our understanding of disease progression in cancer patients and may lead to