Published in final edited form as:

Pediatr Blood Cancer. 2013 May ; 60(5): 748–753. doi:10.1002/pbc.24322.

Does Body Mass Index at Diagnosis or Weight Change During Therapy Predict Toxicity or Survival in Intermediate Risk Rhabdomyosarcoma? A Report From The Children's Oncology Group Soft Tissue Sarcoma Committee

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Abstract

Background—Weight loss prevalence and its impact on toxicities and survival in intermediate risk rhabdomyosarcoma (IRMS) patients are unknown. We evaluated the association between weight change during therapy and number of toxicities, hospital days, infections, and overall survival and between baseline body mass index (BMI) and survival in patients treated on Children's Oncology Group trial D9803.

Procedure—Four hundred sixty-eight IRMS patients age 2 and <21 years treated on D9803 had required data. Regression models evaluated association between weight loss from baseline and toxicities, hospital days, infections, and survival. Kaplan–Meier curves and regression models evaluated baseline BMI percentile's association with survival.

Results—Thirty-five percent and 37% of patients had >5% weight loss at 12 and 24 weeks, respectively, with 16% and 19% losing >10% weight respectively. Greater than 10% weight loss at 24 weeks was associated with more toxicities and hospital days during subsequent therapy but not infection rate or survival. Baseline underweight patients (<5th percentile BMI) had borderline inferior survival compared with baseline average weight patients while there was no difference in survival seen between average weight and overweight or obese patients.

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Additional Supporting Information may be found in the online version of this article.

Conflict of interest: Nothing to declare.

Conclusions—Nearly one in five IRMS patients experienced >10% weight loss on therapy. This was associated with increased toxicity but not decreased survival compared with patients who had less weight loss. Baseline BMI percentile trended toward a significant association with survival. Future studies might investigate nutritional impact on quality of life and if weight loss is preventable by early nutritional intervention.

Keywords

child; nutritional status; rhabdomyosarcoma

INTRODUCTION

Nutritional support has long been considered an important part of supportive oncology care [1,2]. Despite this, there have been very few controlled studies to evaluate what role, if any, nutrition plays in toxicity or survival in the pediatric oncology population. Studies have suggested that malnutrition is quite prevalent. One recent study utilizing highly sensitive measures of nutrition (body cell mass index z-score, percentage body fat, and fat- and fat-free mass as the indicator of nutrition status) found that 45% of patients with cancer were considered malnourished [3]. However the measures used in this study are not commonly used in clinical practice and there is no consensus as to which measure of nutrition is the best to use. It has been suggested that poor nutritional status jeopardizes children with cancer in multiple ways including decreased chemotherapy delivery due to impaired tolerance with resultant inferior overall survival, increased toxicity (specifically infectious toxicity [4]), and decreased quality of life [5].

Several studies have demonstrated an impact of weight on toxicity and survival in the pediatric oncology population. Both overweight and underweight patients with newly diagnosed acute myeloid leukemia (AML) were at increased risk for toxicity and inferior survival (largely due to increased toxic deaths [6]). Similarly, smaller studies evaluating patients with acute lymphoblastic leukemia and metastatic neuroblastoma showed malnourished patients at diagnosis have significantly inferior survival [7–9]. There are no similar studies in children with sarcomas despite literature suggesting patients with solid tumors, including sarcomas, are at particularly high risk for malnutrition based on tumor location/burden and emetogenic therapy [10].

Compromising the analysis of nutrition and outcome in children with cancer is the lack of standardized approaches for evaluating nutritional status or interventions [11]. The nutrition committee of the Children's Oncology Group (COG) surveyed participating institutions on their nutrition practices and 54% of institutions responded. The survey demonstrated great variability among institutions both with regard to timing and type of intervention, with fewer than half of responding institutions reporting a nutrition assessment at time of diagnosis indicating that malnutrition is likely underreported in this population [12].

The primary goal of this study was to determine if there was an association between weight loss while on therapy and toxicity in patients with intermediate risk rhabdomyosarcoma (IRMS) treated on COG trial D9803. Specifically, we examined the number of Grade 3 and 4 toxicities, hospital days, and the number of infections in patients with weight loss (>5% to

10% and >10% weight loss) compared with patients with no more than 5% weight loss [13]. A secondary goal was to determine if there was an association between weight loss while on therapy and overall survival (OS). We chose to evaluate the impact of nutrition on overall survival rather than failure-free survival due to previously published data that patients with recurrent intermediate risk rhabdomyosarcoma have very poor post-relapse survival indicating that overall survival largely recapitulates failure-free survival [14]. Our final goal was to determine if patients who were underweight, overweight, or obese at diagnosis had inferior survival compared with average weight patients as found in the AML population [6].

METHODS

Eligibility criteria for this analysis included patients enrolled on COG D9803 who had weight, height, and toxicity data submitted for evaluation and who were between the ages of 2 and 20 years, as the Center for Disease Control (CDC) has defined BMI-for-age as the standard to assess weight status for children between these ages.

D9803 had three phases [15]. Phase 1 consisted of therapy weeks 0 through 11, phase 2 weeks 12 through 23 and phase 3 weeks 24 through 42 of therapy. Data extracted for this analysis included risk group stratum from the eligibility worksheet and required data from the end of phase reports (EOP). The risk group strata were defined as: stratum 1 = alveolar/undifferentiated (ALV/UDS) Stage 1 Group I; stratum 2 = ALV/UDS Stage 2/3 Group II/III; stratum 3 = embryonal Stage 2/3 Group III; stratum 4 = embryonal Stage 4 Group IV <10 years old; and stratum 5 = parameningeal with extension (PME). Weight and height documented on EOP's at the start of each phase were used to calculate change in weight and BMI from baseline for each of the first two phases. Baseline weight and height were defined as the measurements recorded at the Phase 1 Course 1 EOP. BMI was calculated as weight in kilograms divided by square of the height in meters [16]. Additional data extracted from EOP's included: number of Grade 3 and 4 toxicities, number of days hospitalized, and number of Grade 3 and 4 infections per phase for each patient.

Patients were evaluated based on percent weight change from baseline to determine whether weight loss was associated with excessive toxicity or inferior overall survival. Weight loss was categorized into three categories: weight gain to 5% weight loss, >5% to 10% weight loss, and >10% weight loss.

Descriptive statistics were used to describe patient characteristics. The 12-week (and 24-week) percent weight change from baseline was examined. The analysis was conducted only for patients with weight and height data available at 0, 12, and 24 weeks to calculate change in weight measures and corresponding toxicity data. That is, patients who were alive and on study at 24 weeks (and were not missing height and weight measurements) were included in the analysis of Phase 1 change in weight and its association with Phase 2 outcomes; patients who were alive and on study at 42 weeks (and were not missing height and weight measurements) were included in the analysis of weight change at end of Phase 2 and its association with Phase 3 outcomes.

Negative binomial regression was used to determine if percent weight change at 12 weeks (the end of Phase 1) was predictive of an increased number of Grade 3 and 4 toxicities through 24 weeks (the end of Phase 2) after adjusting for race (white vs. non-white), stratum and baseline weight measurement. The analysis was adjusted for baseline weight because the purpose of the analysis was to examine the change in weight. In this setting, the baseline weight should be included as a covariate in the analysis. Similarly, change in weight from baseline to week 24 was used to predict Grade 3 and 4 toxicities through 42 weeks after adjusting for race, stratum, and baseline weight measurement. A similar analysis was conducted with days hospitalized through 24 weeks (and 42 weeks) as the outcome measure. Logistic regression was used to determine if change in weight at 12 weeks (and 24 weeks) was predictive of increased Grade 3 and 4 infections (dichotomized 0 vs. >0 infections) through 24 weeks (and 42 weeks) after adjusting for race, stratum, and baseline weight measurement. Gender was not included as a covariate because it was not associated with the outcomes. Age is accounted for in the construction of the weight measurements and so is not included separately in the models. ALV/UDS Stage 1 Group I was arbitrarily assigned as the reference group to compare toxicities among the risk strata as it was the first stratum on D9803. Treatment arm was not independently controlled for as there was no significant difference found in toxicity or overall survival between the two chemotherapy regimens [12].

Cox regression models were used to determine if change in weight at 12 weeks (and 24 weeks) was associated with overall survival (OS defined as interval from enrollment to death) after adjusting for baseline weight, race, and risk group stratum. For the analysis of 12-week change in weight in association with OS, the analysis was conducted for patients who were alive and on study at 12 weeks (and not missing height and weight measurements). For the analysis of 24-week change in weight predicting OS, the analysis was conducted only for patients who were alive and on study at 24 weeks (and not missing height and weight measurements).

At diagnosis, CDC standards for BMI by age and gender were utilized to categorize patients as underweight (BMI <5th percentile), average weight (5th to <85th percentile), overweight (85th percentile to <95th percentile) or obese (≥95th percentile). Cox regression analyses were performed in a similar fashion to that outlined above in order to determine if baseline BMI percentile (weight status) was associated with overall survival after adjusting for race and risk strata. Additionally, time to event distributions were estimated using the method of Kaplan and Meier and were compared using the log-rank test for overall survival. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Recruitment and Demographics

There were 488 patients (out of 702 patients on D9803) who fulfilled the eligibility criteria for this analysis. Ninety-one patients under age 2 and five patients greater than 20 years of age were excluded. An additional 20 patients were excluded due to major height inconsistency (defined as EOPs reported patient height increasing by ≥5 cm or decreasing by ≥3 cm between any two phases) leaving 468 patients evaluable for weight change in relation

to toxicity and outcome at baseline. Four hundred thirteen patients were evaluable at week 24 while 401 remained evaluable at week 42 based on required data at the respective time points. Patient and tumor characteristics are shown in Table I.

We found that 9.8% of patients were underweight at baseline while 12.8% were overweight and 11.5% were obese. At 12 weeks into therapy, 19.1% of patients had >5% weight loss from baseline and an additional 15.7% had >10% weight loss. These percentages increased to 18.2% and 18.7% weight loss from baseline, respectively, at 24 weeks. There was a trend to increased incidence of significant weight loss in older patients compared with younger patients and in baseline average weight and obese patients compared with baseline underweight patients at 12 and 24 weeks from baseline (Supplemental Tables I and II.) However, the validity of subset analysis is limited due to small sample size within subsets by age or baseline weight.

Toxicity Outcomes Based on Percent Weight Loss

Percent weight change at week 12 (start of Phase 2) was not associated with Grade 3 and 4 toxicity during Phase 2 for the 413 evaluable patients, after controlling for risk stratum, race and baseline weight (Supplemental Table III). Table II shows the analysis of the 401 patients evaluable for percent weight change at week 24 and its association with Phase 3 and Grade 3 and 4 toxicities. By week 42, there was a trend toward more Grade 3 and 4 toxicities ($P=0.0615$) in patients who lost more than 10% of weight from baseline to week 24. The analysis of percent weight change at week 12 in association with Phase 2 days hospitalized for the 412 evaluable patients demonstrated no association between percent weight loss and days hospitalized (Supplemental Table III). However, there was an association between greater than 10% weight loss at 24 weeks and increased hospital days in Phase 2 after controlling for other variables ($P=0.0463$; Table II). Percent weight change at week 12 and 24 was not associated with an increased number of infections during subsequent phases after controlling for other variables (Supplemental Table III and Table III, respectively).

Survival Based on Percent Weight Loss and Baseline BMI Percentile

Percent weight loss by 12 or 24 weeks was not predictive of overall survival (Table III). Underweight patients at diagnosis had a trend toward inferior OS ($P=0.0596$) when compared with average weight patients at baseline using Cox regression (Table IV). Overweight and obese patients did not have significantly inferior survival compared with average weight patients at baseline using Cox regression (Table IV). Survival was not significantly different among baseline BMI percentile groups ($P=0.19$, log-rank test) as demonstrated in Figure 1.

DISCUSSION

We demonstrated that a large number of patients with intermediate risk rhabdomyosarcoma lose significant weight during therapy, with over one third losing more than 5% and more than one in six losing more than 10% of their baseline weight. This weight loss was not associated with increased Grade 3 and 4 toxicities, infections, or number of hospital days early in therapy. However, by 24 weeks into therapy, patients who lost more than 10% from

baseline were found to have a trend toward increased subsequent Grade 3 and 4 toxicities and significantly more days hospitalized when compared with patients who lost no more than 5% from baseline. We were not able to demonstrate an increased incidence of infections or inferior survival based on weight loss at any time point.

This is the first study to evaluate the association between weight loss and toxicity in a large number of patients with rhabdomyosarcoma to our knowledge. There are two small studies previously published evaluating patients with RMS and infection rate based on nutritional status. One study prospectively evaluated whether total parenteral nutrition (TPN) decreased myelosuppression and infection rates in a group of randomized patients with relapsed sarcomas, including rhabdomyosarcoma (RMS), who were undergoing intensive chemotherapy versus patients who had oral nutrition only. While this study demonstrated improved caloric intake in the TPN treated group, there was no difference between groups in length of myelosuppression, number of transfusions required or infection rates [17]. Another study evaluated 52 children with cancer to determine if nutrition status score correlated with infection rate. While there was a significant inverse correlation between nutritional status and infection rates in the 20 patients with leukemia, there was no association in the 32 solid tumor patients, including a few patients with RMS [18]. Both of these prior studies had smaller sample size, utilized different methods of nutrition assessment, included variable treatment protocols and a mixture of diagnoses with focus on infection as the targeted toxicity. Neither study found an association between nutritional status and infection. Our study addresses these weaknesses by its large sample size and homogeneous population.

We found that 11.5% of patients with IRMS treated on D9803 were obese at diagnosis (>95th percentile) with an additional 12.8% who were overweight (>85th percentile to 95th percentile). These numbers are fairly comparable to current United States statistics that an estimated 17% of children and adolescents are overweight or obese based on the National Health and Nutrition Examination Survey in 2007–2008 [19]. However, 12.8% of patients were underweight (<5th percentile) at diagnosis which greatly exceeds national statistics of less than 5% [20]. These combined numbers for aberrant nutrition are within the range quoted for malnutrition at diagnosis of up to 60% based on diagnosis, site, and extent of disease [3,21] with the expectation that numbers in high risk rhabdomyosarcoma patients would be even higher based on more extensive disease and resultant cachexia. We, however, elected to study the intermediate-risk population rather than the high-risk population, as there are greater numbers of patients to power the analysis and survival rates are so low in the high risk population that analysis of impact of nutrition on events is limited.

We demonstrated that baseline BMI percentile did not have a significant association with overall survival using the log-rank test. However, using Cox regression analysis, underweight patients at diagnosis had a trend toward inferior survival while overweight and obese patients did not have significantly inferior overall survival compared with average weight patients at diagnosis after adjustment for other patient characteristics. The adverse impact of poor nutritional status on outcomes for children with RMS is likely multi-factorial and has direct implications on oncologic management including limiting or delaying chemotherapy due to toxicities from altered drug metabolism or surgical complications, as was seen in a recent retrospective analysis of patients with osteosarcoma that demonstrated

an effect of nutritional status on wound complication rates [22]. Furthermore, significant changes in BMI over a treatment course may alter the radiotherapy dosimetric plan resulting in dose distribution changes that may affect tumor coverage or normal tissue dose exposure. While not as strong of an association as seen in pediatric patients with AML [6], these findings seem to support that nutritional status at diagnosis can impact survival in children with cancer.

There are many other measures of nutritional status, besides weight, and BMI, which have been described as being potentially more informative [23] and could potentially better differentiate patients with jeopardized nutritional status at baseline as well as while on therapy. Such measures could be evaluated prospectively in a sick population over a shorter period of time where it has not been established that BMI is the best indicator for nutritional risk [24]. It is certainly possible that other measures might more accurately reflect true nutritional status. Simultaneous collection of dietary intake data would provide the investigative team with a more comprehensive measure of nutrition status as investigators would gain an understanding of variations in intake of total calories and protein compared to recommended values. Subsequent RMS studies could consider the use of more sensitive indices of nutrition status, such as skinfold tests, combined with dietary intake information of the prospective population to evaluate whether nutrition impacts toxicity and/or survival.

This study does not take into account institutional variability with nutrition intervention. It is possible that the number of patients malnourished was deflated due to proactive placement of feeding tubes or use of TPN thus limiting our power to determine an effect of malnutrition on the primary study goals. As there is known great variability [13], a future analysis might evaluate the association between interventions (days on TPN or nasogastric/orogastric feeds) and weight loss and/or outcomes. It is important to determine if weight loss is modifiable with early intervention. An additional question is whether toxicity in patients with weight loss despite aggressive intervention is distinct from toxicity in patients with weight loss who do not receive intervention. One must consider that nutrition intervention might not only diminish weight loss but also modify other parameters such as immunologic status due to improved micronutrient exposure that could impact toxicity independent from weight loss [25].

Finally, this study demonstrates that weight loss is quite prevalent in this population and, therefore, warrants attention early to minimize the morbidity of weight loss as an independent toxicity of rhabdomyosarcoma and its therapy. We had no ability to measure how weight loss impacts quality of life in this retrospective analysis, but it is an important question to answer prospectively. Malnutrition in oncology is a very complex subject that must take into account tumor burden, cancer-cachexia syndrome, therapy-induced nausea, fear of emesis with resultant food avoidance, mucositis, changes in taste/smell, food aversion related to the texture, taste, sight or smell of food, parent/child conflict over eating, body image concerns, resistance to placement of nasogastric, or gastrostomy tubes, and potentially other confounding factors. However, the prevalence of malnutrition previously published and the weight loss demonstrated in this study highlights the need to include nutrition questions in future studies, as the literature suggests weight loss may significantly impact quality of life. Several ongoing clinical trials have quality of life questionnaires as

part of the study. Similar future studies could include questions addressing weight, eating habits, food attitudes, and barriers to nutrition in order to get a better idea of how nutrition is jeopardized and result in a better understanding of potential targets for intervention studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
OS, baseline BMI.

TABLE I**Baseline Patient Characteristics, Categorical Data**

Characteristic	Count (n = 468)	Percent
Age		
2–9	317	67.74
10+	151	32.26
Sex		
Male	296	63.25
Female	172	36.75
Race		
Black	61	13.03
Hispanic	55	11.75
Other	31	6.62
White	321	68.59
Stage (composite)		
1	55	11.75
2	127	27.14
3	251	53.63
4	35	7.48
Group (composite)		
I	26	5.56
II	53	11.32
III	354	75.64
IV	35	7.48
Primary site		
Extremity	66	14.10
GU B/P	62	13.25
Other	83	17.74
PM	190	40.60
Retro/Per	67	14.32
Histology (composite)		
RMS/NOS	23	4.93
Alv	208	44.33
Emb	223	47.75
Undif	14	3.00
Treatment assignment		
VAC	196	41.88
VAC/VTC	182	38.89
PMext VAC	90	19.23
Strata		
ALV/UDS, Stage I or Group I	66	14.10
ALV/UDS, other patients	135	28.85

Characteristic	Count (n = 468)	Percent
Emb, Stage 2/3, Group III	151	32.26
Emb, Group IV, age < 10	26	5.56
PM, with extension	90	19.23
Phase 1/Course 1 BMI		
<5%	46	9.83
5% to <85%	308	65.81
85% to <95%	60	12.82
95%	54	11.54

TABLE II

Adjusted Odds Ratios* for the Effect of 24-Week Percent Weight Change on Toxicity at 42 Weeks (Grade 3 and 4 Toxicities, Hospitalizations, and Infections)

Reference group: <5% weight loss	24-week percent weight change predicting Grade 3 and 4 toxicity at 42 weeks	24-week percent weight change predicting hospitalization at 42 weeks	24-week percent weight change predicting infection at 42 weeks
n	401	401	401
>5% to 10% vs. <5% weight loss			
Odds ratio (95% CI)	1.01 (0.86, 1.17)	0.93 (0.75, 1.15)	1.43 (0.79, 2.61)
P-value	0.94	0.51	0.24
>10% vs. <5% weight loss			
Odds ratio (95% CI)	1.16 (0.99, 1.35)	1.24 (1.00, 1.54)	0.92 (0.52, 1.63)
P-value	0.06	0.046	0.77

CI, confidence interval; P1, Phase I; C1, Course 1.

* Adjusted for age, P1/C1 weight, sex, race, and treatment strata.

TABLE III

Adjusted Hazards Ratios* for the Effect of Percent Weight Change on Overall Survival

Reference group: <5% weight loss	12-week percent weight change predicting survival	24-week percent weight change predicting survival
n	411	398
>5% to 10% vs. <5% weight loss		
Hazards ratio (95% CI)	0.54 (0.28, 1.03)	1.15 (0.66, 2.01)
P-value	0.06	0.61
>10% vs. <5% weight loss		
Hazards ratio (95% CI)	0.79 (0.43, 1.47)	0.66 (0.33, 1.29)
P-value	0.46	0.23

CI, confidence interval; P1, Phase 1; C1, Course 1.

* Adjusted for age, P1/C1 weight, sex, race, and treatment strata.

TABLE IV Adjusted Hazard Ratios ^{*} for the Effect of Baseline BMI on Overall Survival

Reference group: Average weight (BMI 10–85th percentile)	Baseline BMI predicting overall survival
n	468
<10th percentile	
Hazard ratio (95% CI)	1.70 (0.98, 2.96)
<i>P</i> -value	0.06
>85th percentile to 95th percentile	
Hazard ratio (95% CI)	1.28 (0.73, 2.25)
<i>P</i> -value	0.38
>95th percentile	
Hazard ratio (95% CI)	0.98 (0.51, 1.87)
<i>P</i> -value	0.95

CI, confidence interval; P1, Phase 1; C1, Course 1.

^{*} Adjusted for age, P1/C1 weight, sex, race, and treatment strata.