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AnthropomorphicMeasurements and Event Free Survival in Patients with Favorable Histology Wilms Tumor:

A Report from the Children's Oncology Group

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Abstract

PURPOSE—We retrospectively examined the effect of body weight and body mass index (BMI) on event-free survival (EFS) of children with Wilms tumor treated on National Wilms Tumor Study-5 (NWTS-5).

PATIENTS AND METHODS—Eligible study participants: Stage I - IV favorable histology Wilms tumor with immediate nephrectomy; height and weight recorded at diagnosis, and loss of heterozygosity for chromosomes 1 p and 16 q assessed.

RESULTS—A total of 1,532 patients were included in the analysis. The median follow-up was 4.9 years. 493 patients were less than 2 years of age and 1039 were 2 years of age or older. In both age groups there were more patients than expected with a weight or body-mass-index (BMI) less than the 10%ile or greater than the 90%ile. There was no relationship of weight-for-age or BMI-for-age and EFS in univariate analyses (p=0.28, log-rank test for both comparisons). A Cox proportional hazards model, stratified by risk/treatment groups, showed that, among patients less than 2 years of age, low or high weight-for-age was not predictive of EFS (p=0.16). Similarly, a Cox proportional hazards model, stratified by risk/treatment groups, showed that among patients greater than 2 years of age, low or high body mass index for age was not predictive of EFS (p=0.58).

CONCLUSIONS—There was no evidence that anthropomorphic data obtained at diagnosis for patients with favorable histology stage I - V Wilms tumor was predictive for EFS in the setting of current treatment regimens. There were more patients with lower or higher weight/BMI than expected.

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Keywords

Wilms; body mass index; prognosis

Introduction

Children with favorable histology (FH) Wilms tumor (WT) have excellent event-free survival (EFS) and overall survival. A number of important prognostic features have been identified including age, stage, tumor weight and loss of heterozygosity for chromosome 1p and 16q [1,2]. There remains a group of patients who have an inferior EFS in the absence of known prognostic features.

Understanding of the potential contribution of high or low BMI to outcomes for children with cancer is increasing. A recent study of children with acute myeloid leukemia demonstrated that both underweight (<10th percentile BMI) and overweight (>95th percentile BMI) were associated with an excess in treatment-related complications resulting in significantly reduced survival [3]. Children who are underweight with acute lymphoblastic leukemia or solid tumors may experience an increased risk for relapse and decreased survival [4], although this has recently been questioned in a review of St. Jude Children's Research Hospital leukemia trials [5]. It is of note that these findings are in contrast to the adult population where underweight is not associated with increased mortality and overweight is associated with excess relapse rather than toxicity [6].

The few studies relating body mass index to outcome in children with WT are limited by the size of the cohorts studied. A study of 20 children with advanced stage WT suggested an increase in drug toxicity for those who were lower weight-for-height [7]. Another study, conducted in South Africa, demonstrated no effect of low weight (< 3%) or low weight-for-height on the morbidity of treatment or survival in 59 children with a mixture of stages of FH WT [8]. Interpretation of this study was limited by the relatively small numbers and a higher number of advanced stage patients. Donaldson demonstrated improved survival related to good nutritional status in children with solid tumors but only six of the cases described in that study were WT [9].

Identification of BMI- or weight-for-age as a prognostic factor would be an important step to potential targeting of therapy. If found to predict an inferior survival, further work would need to examine if this observation was related to somatic host factors such as altered pharmacodynamics or genetic host factors, such as drug-metabolizing or growth factor polymorphisms, that might also segregate with BMI or weight. We evaluated data from a large cohort (NWTS - 5) to determine if BMI-for-age or weight-for-age was an independent prognostic factor for EFS in children with stage I - IV FH WT.

Patients and Methods

NWTS 5 was a prospective trial designed to study the prognostic importance of loss of heterozygosity (LOH) for chromosomes 1p and 16q using single arm, standard treatment regimens for patients classified by stage and histology with WT conducted by the National Wilms Tumor Study Group. The study was open for accrual from August 1995 to June 2002. Participating institutions secured local institutional review board approval for the conduct of the study. Patients were enrolled after provision of informed consent by a parent or legal guardian. This report utilizes only secondary analysis of original data. Patients were eligible for NWTS 5 if they had received no prior chemotherapy or radiotherapy, had an institutional histological diagnosis of WT, clear cell sarcoma of the kidney or rhabdoid

tumor of the kidney. Participants underwent nephrectomy if technically feasible, or biopsy, followed by appropriate therapy determined by stage and age, and by weight of the tumor for very low risk patients.

For the purpose of this analysis, eligible study participants included post-nephrectomy patients enrolled on NWTS - 5 of any age with stage I - IV FH WT who had: 1. recorded height and weight at diagnosis post-nephrectomy; and 2., evaluable data regarding loss of heterozygosity for chromosomes 1 p and 16 q.

The calculation of body mass index percentile for age (based on year 2000 growth charts) was performed using software available from the Centers for Disease Control (CDC) and Prevention (gc-calculate-BIV.sas: see http://www.cdc.gov/nccdphp/dnpa/growthcharts/sas.htm)[10]. This calculation is valid only for age greater than 2 years. Children less than 2 years had their weight-for-age percentiles assigned per CDC growth charts published in May 2000 [11].

Statistics

Event-free survival was defined as the time from study entry to the first occurrence of disease progression or death as a first event. Follow-up for patients not experiencing an event was censored at the date of last contact. The relationship of weight percentile-for-age (age less than 2 years) or BMI percentile-for-age (age 2+ years) and event-free survival was first assessed using the log-rank test. Multivariate analyses using the Cox proportional hazards model were then performed assessing the influence of weight or BMI on outcome. In these analyses, patients were stratified by disease stage and the chemotherapy protocol delivered [EE4A = vincristine/dactinomycin] [DD4A = vincristine/ doxorubicin/ dactinomycin] [12]. The analyses used in this report utilize the overall stage provided at the institutional level. Indicator variables were used to define less than 5%, 5-9.9%, 90-94.9% and 95+% weight and BMI subsets. The estimated relative risks for the <10% and >90% weight percentile-for-age subsets (compared to the subset with weight percentiles between 10-89.9%) were calculated for patients less than 2 years of age. Similar calculations were made for the relative risks for the BMI percentile-for-age subsets for patients 2 years of age or older.

Results

Patient Characteristics

2,596 patients were enrolled on NWTS - 5, of whom 1,814 had FH WT, of whom 1,532 met the additional eligibility criteria. The clinical characteristics of age, stage distribution and therapy are shown in Table I for those less than 2 years of age and Table II for those greater than or equal to 2 years of age. The median follow-up at the time of the analysis was 4.9 years.

Age less than 2 years at diagnosis (n= 493)

The percentile distribution of weights observed in our patients studied did not match the expected distribution of values based on the CDC year 2000 growth charts applicable to all ethnicities. 78 patients (15.8%) had a weight-for-age below the 10^{th} %tile and 75 patients (15.2%) had a weight-for-age above the 90^{th} %tile ($p<0.001$). 10% had a weight-for-age percentile of 5.6 or below and 10% had a weight-for-age percentile of 93.4 or above. One of these low weight patients had WAGR syndrome. A total of 17 patients were reported by the local institution to have an overgrowth syndrome (3%). Seven were classified as Beckwith-Wiedemann syndrome, 8 with hemihypertrophy and 2 with both. As expected most of those (65%) identified with an overgrowth syndrome had weight for age > 90%tile. In addition, 62

patients (13%) had perilobar nephrogenic rests (reported to be associated with high birth weights[13]), 10 (16%) of whom were at or above the 90% of weight for age. However 65/424 (15%) of patients without perilobar nephrogenic rests were also at or above the 90% of weight for age. Unilateral left sided WT was seen in 262 of the 493 (230 right sided, 1 'unknown'). Seventeen percent (17%) of patients with left sided tumors were less than the 10%tile in weight; the percentage was 14% for right sided tumors in 14% (p=0.46).

A univariate analysis of the relationship of weight- for-age using the 8 groups defined in Table III and EFS showed no statistical evidence for a relationship (p=0.28, log-rank test). A Cox proportional hazards model was fitted, stratifying on disease stage and treatment received and including indicators for the less than 5%, 5-9.9%, 90-94.9% and 95+% subsets. After adjusting for stage and treatment groups, the EFS experience for those in the four low or high weight-for-age categories were not statistically significantly different from those in the 10-89.9% subset (p=0.16). Relative risks for EFS are shown in Table IV.

Age greater than or equal to 2 years at diagnosis (n= 1039)

The percentile distribution of BMI observed in patients 2 years of age and older at diagnosis demonstrated more patients with lower and higher BMIs than expected as compared to the CDC year 2000 growth charts. 158 patients (15%) had a BMI-for-age below the 10^{th} %tile ($p<0.00001$) and 137 patients (13%) had a BMI-for-age above the 90^{th} %tile ($p<0.001$). We noted that 10% had a BMI-for-age percentile of 4.7 or below and 10% had a BMI-for-age percentile of 92.5 or above (V). One of these low BMI patients had WAGR syndrome. A total of 25 patients were reported by the local institution to have an overgrowth syndrome (2%). Twelve were classified as Beckwith-Wiedemann syndrome, 7 as hemihypertrophy and 3 as both. Nearly one-half (10/22, 48%) of those identified with an overgrowth syndrome had BMI for age > 90%tile. A total of 218 (22%) of greater than 2 year old patients had perilobar nephrogenic rests (30 unknown). Fifteen percent (15%) of patients with perilobar nephrogenic rests had BMI at or above the 90^{th} percentile; the percentage for patients without perilobar nephrogenic rests was 12%. Unilateral left sided WT was seen in 590 of the 1198 (537 right side, 64 bilateral, 12 'other' and 1 missing). Excluding bilateral and other tumors, for those patients < 10%ile in BMI for age, left sided tumors were found in 15% and right sided tumors in 15% (p=0.60).

A univariate analysis of the relationship of BMI-for-age and EFS showed no statistical evidence for a relationship (p=0.52, log-rank test). A Cox proportional hazards model was fitted, stratifying on disease stage and treatment received and including indicators for the less than 5%, 5-9.9%, 90-94.9% and 95+x% subsets. There was no evidence that, after adjusting for risk groups that low or high weight-for-age was predictive of outcome for these patients (p=0.71). Relative risks for event free survival are shown in Table VI.

Discussion

We were unable to identify either low or high weight- or BMI-for-age as prognostic factors for EFS in patients with FH WT in our very large cohort. This is in contrast to pediatric patients with acute myeloid leukemia and possibly in other pediatric cancers. For the subgroup of patients under 2 years of age, however, the width of the confidence intervals shown in Table IV makes clear that this study was not sufficiently powered to rule out the types of weight effects observed in other studies.

Underweight (body mass index [BMI] <18.5) and obesity (BMI >30) are associated with excess mortality from all causes in adults greater than 25 years of age [14,15]. A number of studies in adult oncology cohorts have documented an association between obesity and inferior survival in women with breast cancer and colon cancer [16-18] and on local

recurrence in males with rectal cancer[18]. There is conflicting evidence with respect to the contribution of excess toxicity to an overall inferior mortality seen in patients with obesity [19,20].

The correlation between underweight and inferior outcome in some malignancies has a number of different potential explanations including increased toxicity and altered drug metabolism. A study in leukemia patients suggested that toxicity and relapse were not associated with BMI in a developed world setting [5]. It is possible that more severe malnutrition may adversely affect outcomes. We are unable to determine if the lack of impact of low weight at diagnosis upon outcome was related to intensive nutritional intervention, as these data were not recorded on NWTS 5. Rickard examined 31 malnourished children with newly diagnosed WT in the Third National Wilms Tumor Study protocol [21]. In patients who were termed high nutritional risk, adequate parental nutrition support reversed protein energy malnutrition and prevented chemotherapy and radiotherapy delays due to granulocytopenia.

Increased birth weight is associated with an excess risk for the development of certain cancers including WT [22,23]. This is postulated to be related to growth factor excess. Overweight in normal children and adolescents without cancer has a variety of adverse health outcomes including Type II diabetes, obstructive sleep apnea, dyslipidemia, fatty liver disease and hypertension [24]. All of these may decrease tolerance to complete chemotherapy delivery. In contrast to underweight patients, it is unlikely that nutritional interventions had a substantial impact upon the EFS given the relatively short time frame of therapy for WT (18-24 weeks). While excess drug toxicity in overweight patients may be related to altered metabolism, for example by prolonged clearance of doxorubicin [25,26], it is possible that any altered metabolism is not sufficient to produce a detectable difference in EFS in a highly curable tumor such as WT.

We did not expect to find an excess of both high and low weight or BMI patients as compared to the CDC 2000 charts. Between 20-30% of those who were overweight at diagnosis may be explained by overgrowth syndromes or the known association of overweight with perilobar nephrogenic rests. An excess number of patients with high birth weight has previously been identified in WT, neuroblastoma and leukemia and it is possible that this anthropomorphic characteristic persists as the child matures [22]. Likewise, the excess in low weight or BMI is inadequately explained by syndromes, such as WAGR or birth weight. We found no evidence that the excess in lower weight and BMI was explained by compromised nutrition secondary to a direct mass effect of left sided WTs on the stomach. Weight loss post-operatively and tumor-induced cachexia due to increased tumor related catabolism may also contribute to this finding.

Strengths of this secondary analysis study are that this represents the largest prospectively collected cohort used to study this question. Patients had central review histology to confirm diagnosis. Limitations include that we do not have information about any nutritional interventions that may have been implemented for this group of patients. There are also inherent possible errors in taking and recording anthropomorphic measurements, although there is unlikely to be a systematic bias in over- or under-estimating measurements.

Weight or BMI as a prognostic factor for children with FH WT would have potential significance as it is easily measured, and thus available at the time of protocol initiation[27]. We found no evidence that such a prognostic factor exists in our cohort.

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Table I

Clinical characteristics of favourable histology Wilms patients less than 2 years of age at diagnosis described by risk group, stage and final treatment regimen on NWTS 5

Risk group	*Total Number*	*Number by treatment*	*5 yr EFS*	**95% Confidence intervals**
Very Low (Stage I, tumor wt <550 gm)	198	N=122 EE4A N=76 no chemo	93%	89%, 96%
Low (Stage I > 550 gm, Stage II)	206	N=206 EE4A	87%	82%, 91%
Standard (Stage III, IV)	89	N= 9 EE4A N=80 DD4A	82%	72%, 89%

a. Age < 2 years at diagnosis (n= 493)

Table II

Clinical characteristics of favourable histology Wilms patients greater than or equal to 2 years of age at diagnosis described by risk group, stage and final treatment regimen on NWTS 5

Risk group	*Total Number*	*Number by treatment*	*5 yr EFS*	**95% Confidence intervals**
Low risk (Stage I, stage II)	542	N=542 EE4A	87%	84%, 89%
Standard risk (Stage III, IV)	497	N=497 DD4A	83%	80%, 87%

a. Age > or = 2 years at diagnosis (n=1039)

Table III

Distribution of weight percentile for patients with FH Wilms tumor less than 2 years of age at diagnosis treated on NWTS-5

Percentile of Distribution	Number of patients observed	Number of patients expected
Less than 5%	45	25
5-9.9%	33	25
10-24.9%	64	74
25-49.9%	96	123
50-74.9%	114	123
75-89.9%	66	74
90-94.9%	35	25
More than 95%	40	25

Table IV

Estimated relative risk of relapse by high or low weight- for- age percentile subsets compared to a subset of patients with a weight between 10-89.9%ile in Wilms tumor patients less than 2 years of age at diagnosistreated on NWTS-5 (adjusted for stage and treatment)

Percentile subset	Number	Estimated relative risk of relapse	95% confidence intervals for RR	P value	Number of observed failures
Less than 5%ile	45	1.93	0.93, 4.03	0.08	9
5-9.9%ile	33	0.91	0.28, 2.99	0.87	3
10-89.9%ile	340	1.00			37
90-94.4%ile	35	0.24	0.03, 1.75	0.16	1
More than 95%ile	40	1.02	0.36, 2.87	0.97	4

Table V

Distribution of body mass index percentile for patients with FH Wilms tumor greater than or equal to 2 years of age at diagnosis treated on NWTS-5.

Percentile of Distribution	Number of patients observed	Number of patients expected
Less than 5%	106	52
5-9.9%	52	52
10-24.9%	140	156
25-49.9%	184	260
50-74.9%	232	260
75-89.9%	188	156
90-94.9%	62	52
More than 95%	75	52

Table VI

Estimated relative risk of relapse by high or low body mass index (BMI)- for- age percentile subsets compared to a subset of patients with a BMI between 10-89.9%ile)in Wilms tumor patients greater than or equal to 2 years of age at diagnosis treated on NWTS-5 (adjusted for stage and treatment)..

Percentile subset	Number	Estimated relative risk of relapse	95% confidence interval	P value	Number of observed failures
Less than 5%ile	106	0.85	0.49,1.49	0.85	14
5-9.9%ile	52	0.77	0.34,1.74	0.52	6
10-89.9%ile	744	1.00			115
90-94.4%ile	62	0.72	0.34, 1.54	0.40	7
More than 95%ile	75	0.61	0.29, 1.31	0.21	7