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A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Megestrol Acetate as an Appetite Stimulant in Children With Weight Loss Due to Cancer and/or Cancer Therapy

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Background. Megestrol acetate (MA) is an appetite stimulant with efficacy in promoting weight gain in adults with cancer-associated anorexia–cachexia. Studies documenting MA efficacy in children, however, are limited. We present the first randomized, double-blind, placebo-controlled clinical trial of MA versus placebo in children with cancer and weight loss. ***Methods.*** Subjects <18 years of age with weight loss (minimum 5% from highest previous weight; or %ideal body weight <90%) due to cancer and/or cancer therapy were randomized to either MA (7.5 mg/kg/day) or placebo for a planned study duration of 90 days. Primary outcome was the difference between groups in mean percent weight change from beginning to end of the study period. Secondary outcomes included effects on anthropometrics, body composition, need for tube feeding or parenteral nutrition, and toxicities. ***Results.*** Twenty-six patients were randomly assigned (13 MA, 13 placebo). The MA group experienced a mean weight gain of +19.7% compared to a mean weight loss of −1.2% in the placebo group, for a difference of +20.9% (95%CI: +11.3% to +30.5%, $P = 0.003$) in favor of MA over placebo. MA subjects experienced significant increases in weight for age z-scores, body mass index z-scores, and mid upper arm circumference compared to placebo. DXA scanning suggested disproportionate increases in fat accrual. Adrenal suppression was the main toxicity of MA. ***Conclusion.*** In children with high-risk malignancies, MA resulted in significant increases in mean percent weight change compared to placebo. Further studies of MA should be pursued to better delineate the effect on nutritional status. Pediatr Blood Cancer 2014;61:672–679.

Key words: appetite stimulant; megestrol acetate; pediatric cancer; randomized trial; weight loss

INTRODUCTION

Malnutrition and weight loss are common complications of cancer and cancer therapy in children [1]. Adverse outcomes associated with malnutrition include treatment intolerance [2], delays in therapy [3], increased infections [4], reduced quality of life [5], and inferior survival [6,7]. Supplemental nutritional support, including enteral tube feeding and parenteral nutrition (PN), remain the primary interventions for children with poor nutrition [2,8]. These therapies have complications however, including risk of infection and cholestasis with long-term PN. Poor cosmetic appeal, nasopharyngeal irritation, and need for tube reinsertion limit tolerance of enteral tube feeding in children, particularly adolescents.

Appetite stimulants have received little attention as potential therapies for pediatric oncology patients with weight loss. Megestrol acetate (MA) is a progestational agent with appetite stimulating properties, with demonstrable ability to increase weight in adults with cancer-associated anorexia and cachexia [9]. Ease of administration and a low side effect profile are good reasons why MA could offer an attractive adjunct or alternative to supplemental nutritional support in children with cancer and weight loss. Pediatric studies of appetite stimulants, however, have been limited to case series and historical cohort studies without placebo controls [10,11], making it difficult to draw firm conclusions regarding their efficacy in promoting weight gain in children. We present the first randomized, placebo-controlled trial of MA in children with weight loss due to cancer and/or cancer therapy. This pilot clinical trial was designed to determine if relatively large increases in weight could be obtained with MA compared to placebo.

METHODS

Eligibility

Subjects were <18 years of age with a malignant diagnosis and weight loss secondary to cancer and/or cancer treatment. At the time of enrollment participants had to have lost ≥5% body weight from their previously recorded highest weight between diagnosis and study entry, or have a history of anorexia and a % ideal body weight (actual body weight divided by ideal body weight for height × 100%) <90% for age and gender [12]. Subjects must have been able to eat orally and were receiving active treatment or palliative therapy with a life expectancy of at least 3-months. Exclusion criteria included: (1) nasogastric, nasojejunal, gastrostomy tube feeding, or parenteral nutrition (PN) at the time of study enrollment, (2) systemic corticosteroid administration within 14 days preceding enrollment, (3) anticipated administration of >7 days of systemic corticosteroids (except for anti-emetic control) in any 6-week block during the study, (4) pre-existing hyperglycemia, (5) pre-existing adrenal insufficiency (defined as an 8:00 AM

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serum cortisol lower than age-adjusted normal limits with confirmation by ACTH stimulation testing), (6) a previous or concurrent thromboembolic condition (deep venous thrombosis, cerebrovascular accident), and (7) pregnancy. The trial was approved by the research ethics boards of the Universities of Alberta and British Columbia and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice [13]. Informed consent was obtained from parents or guardians, and patient assent was obtained when appropriate. The trial was registered on ClinicalTrials.gov (identifier: NCT00439101).

Study Design, Evaluations and Treatment Plan

This was a randomized, double-blind placebo-controlled investigator-initiated trial performed at the Stollery Children's Hospital (SCH) (University of Alberta, Edmonton) and the British Columbia Children's Hospital (BCCH) (University of British Columbia, Vancouver). Participants were randomly assigned 1:1 to MA suspension (7.5 mg/kg/day, maximum 800 mg/day) or an equivalent volume of placebo (identical in taste, smell, and appearance). The anticipated study duration was 90 days. A computer generated block randomization list using random-number generating software was created, with block size varying between four and six to limit investigator's ability to predict the assigned arm.

Baseline and end-of-study evaluations included review of the diagnosis and treatment, weight, height, mid-upper arm circumference (MUAC), triceps skin fold (TSF) thickness, dual energy X-ray absorptiometry (DXA) scans for body composition analysis, blood glucose and 8:00 AM cortisol levels. Trained dietitians measured MUAC and TSF using standard techniques [14]. MUAC was measured to the nearest 0.1 cm at the midpoint of the upper arm, halfway between the acromion and olecranon. TSF was measured by locating the midpoint of the upper arm, grasping a vertical fold of skin plus underlying fat 1 cm above, and gently pulling the fold away from the muscle. Calibrated calipers (Lange at SCH; Harpenden at BCCH) were then applied at right angles 1 cm below the grasp, with the measurement taken to the nearest 0.1 mm. MUAC and TSF were taken in triplicate and averaged. Each subject used the same DXA machine and software for baseline and end-of-study evaluations; however, the two hospitals used different equipment (Lunar Prodigy at SCH; Hologic at BCCH).

Participants' weight was monitored on a regular basis (minimum every 2-weeks). Side effect profiles and compliance was monitored every 4-weeks. Blood glucose and 8:00 AM cortisol levels were drawn at 2- and 4-weeks into the study, and monthly thereafter. Specific toxicities of MA monitored for included adrenal suppression, hyperglycemia, and venous thromboembolism. Toxicities were graded as mild, moderate, or severe according to criteria previously published [15], and as not related, possibly, probably, or definitively related to the study treatment.

Subjects were allowed nutritional supplementation by mouth only. Concurrent use of other appetite stimulants was prohibited. Dose reductions (25% decrements in volume) for concerns of excessive hunger were allowed at parental or patient request. Dose escalation for lack of appetite was not allowed. Pre-defined rules for withdrawing a participant before 90 days included: (1) ongoing weight loss to $\geq$15% of the highest pre-study weight, which was a criterion to start tube feeds or PN, (2) fasting blood glucose levels $>$10 mmol/L or symptomatic hyperglycemia, (3) severe, clinically relevant adrenal suppression defined as low 8:00 AM serum cortisol levels along with hypotension or cardiovascular compromise requiring stress-doses of hydrocortisone, (4) any toxicity deemed severe and potentially related to the study (resulting in premature unblinding for safety reasons), (5) non-compliance. Initiation of tube feeds or PN was not allowed until the stopping rule of $\geq$15% weight loss was met.

Statistical and Data Analysis

Randomized participants who took any amount of the assigned treatment (even if less than 90 days) were included in the baseline and follow-up data analysis. Change in weight over the study period was measured as a percentage for each participant: (end study weight divided by initial weight at enrollment) $-$ 1 $\times$ 100%. End study weight was measured as close to, but within 7 days of the last administered dose. For the MA and placebo groups, mean percent weight change (sum of individual percent weight changes divided by the number of participants in each group) and standard deviations were calculated. The primary outcome was the difference in mean percent weight change between the MA and placebo arms. A relatively large difference of at least 10% between the groups was felt to be the minimum to be considered potentially clinically relevant. Assuming a 15% loss to follow-up, and using estimated percent weight change standard deviations of 8% (MA) and 5% (placebo) from previously reported pediatric studies of MA in non-oncology populations [16–19], a sample size of 26 provided 90% power with a two-sided $\alpha = 0.05$ to detect a statistically significant difference between the groups. Secondary outcomes included differences in the magnitude of change for weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ), and body mass index-for-age z-scores (BMI-Z) over the study period; end study weight relative to the highest previously recorded weight before study enrollment (percentage change); the number of subjects needing to be withdrawn early from study to initiate tube feeds or PN for ongoing weight loss; changes in body composition by anthropometrics and DXA scanning; and toxicity.

WAZ, HAZ, BMI-Z were calculated using Epi-Info 2000 (Centers for Disease Control) [20]. Z-scores for body composition measurements were compared to pediatric population and equipment-specific normative data (Lunar Prodigy [21]; Hologic [22]).

Means and standard deviations are presented. Two-tailed *t* tests (for equal and unequal variances where appropriate) compared outcomes between the two groups. Bonferroni correction was used for comparisons of weight and BMI outcomes. Fisher's exact tests were used to compare decreases in prescribed volume, meeting stopping rules, and presence of low cortisol levels.

RESULTS

Twenty-six subjects were enrolled and randomly assigned (13 MA, 13 placebo) between September 2003 and November 2011 at SCH (n = 11) and BCCH (n = 15). All 13 MA and 10/13 placebo subjects received their allocated treatment and had adequate baseline and follow-up data for analysis (Fig. 1). Two eligible placebo subjects, both of whom initially agreed to participate, failed to take any of the assigned treatment after randomization resulting in no follow-up data. Data from these two subjects is included in the baseline but not follow-up data. A third placebo subject was determined to be ineligible just after enrollment and randomization (failed ACTH stimulation test). This participant did not receive any

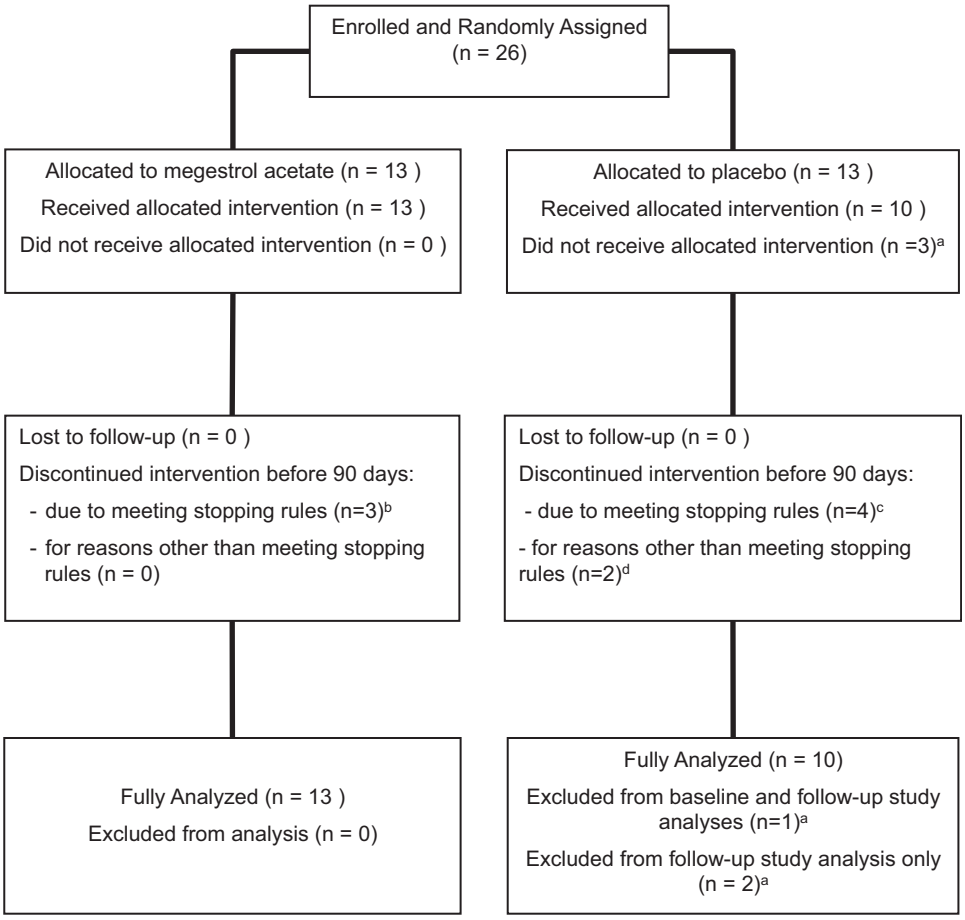

Fig. 1. Consort flow diagram. Explanations: (**a**) Two eligible subjects randomized to placebo failed to be compliant with any of the assigned treatment and had no adequate follow-up data. Since these subjects were originally eligible for study, they are included in baseline but not follow-up data analysis. One additional subject was enrolled and randomized to the placebo arm, but was later found ineligible due to a failed ACTH stimulation test at baseline. This subject is not included in baseline or follow-up data analysis, given they were not eligible for the study. (**b**) Reason and day of study removal: non-compliance (Day 69), adrenal suppression requiring hydrocortisone during sepsis (Day 56 and 67). **(c)** Reason and day of study removal: parental request to withdraw (Day 69), weight loss $\geq$15% (Day 18, 30, 36). **(d)** Two subjects randomized to placebo started PN for clinical reasons despite not losing 15% weight at discretion of attending physician, necessitating withdraw from study (Day 55 and 59). End-study evaluations were available and analyzed at time of initiation of PN.

study medication and is not included in the baseline or follow-up data analysis. The median number of days on-study for the MA group was 90 days (range 56–90 days) compared to 55 days (range 18–90 days) in the placebo arm. Seventy-seven percent (10/13) of the MA group completed the full 90-day study period, compared to 33.3% (4/12) in the placebo arm (OR: 6.67; 95%CI: 1.14–38.83; $P = 0.035$). Among subjects initiating and completing the study, compliance was good. Three subjects on the MA arm missed an estimated 2 days (surgery), 30 days (parental separation), and 32 days (unknown reason, subject withdrawn at day 69 for non-compliance), while one subject on the placebo arm missed an estimated 12 days for perceived irritability before being withdrawn at parental request. The remainder of participants described full compliance on follow-up reporting.

Demographics

Heterogeneity in cancer diagnosis was observed between arms; however, all cases were considered high-risk malignancies and/or included intensive therapies (Table I). No other differences in demographics or patient characteristics existed between groups at baseline.

Primary Outcome: Change in Percent Weight

Over the study period, the MA group experienced a mean weight gain of +19.7% (±15.3%) compared to a mean weight loss of −1.2% (±4.9%) in the placebo arm, representing a statistically significant difference in mean percent weight change of +20.9% (95%CI: +11.3% to +30.5%, $P = 0.003$) in favor of MA over placebo (Fig. 2A, Table II).

Secondary Outcomes: Other Weight and Anthropometric Measures

Mean WAZ increased significantly for the MA group compared to placebo ($+1.00 \pm 0.79$ vs. -0.18 ± 0.34, respectively; difference +1.18 in favor of MA; 95%CI: +0.67 to +1.70, $P = 0.002$)

TABLE I. Baseline Patient Demographics and Clinical Characteristics

Characteristic	MA arm (n = 13) No. (%)	Placebo arm (n = 12)[a] No. (%)	*P*	Placebo arm (n = 10)[b] No. (%)	*P*
Age, years					
Median	9.7	12.5	0.45	10.9	0.74
Range	1.1–17.8	3.9–16.2		3.9–16.2	
Sex					
Male	7 (53.8)	5 (41.7)	0.70	3 (30.0)	0.40
Female	6 (46.2)	7 (58.3)		7 (70.0)	
Diagnosis					
Osteosarcoma	1 (7.7)	3 (25.0)		1 (10.0)	
Ewing Sarcoma	1 (7.7)	1 (8.3)		1 (10.0)	
Medulloblastoma/PNET	5 (38.5)	2 (16.7)		2 (20.0)	
High-risk neuroblastoma	1 (7.7)	2 (16.7)		2 (20.0)	
AML	2 (15.4)	2 (16.7)		2 (20.0)	
ALL (relapsed)	1 (7.7)	0 (—)		0 (—)	
Stage IV Hodgkin lymphoma	1 (7.7)	0 (—)		0 (—)	
Lymphoblastic Lymphoma	0 (—)	1 (8.3)		1 (10.0)	
Rhabdomyosarcoma	1 (7.7)	0 (—)		0 (—)	
Metastatic germ cell tumor	0 (—)	1 (8.3)		1 (10.0)	
Weight at study entry, kilograms					
Mean	33.6	40.1	0.59	33.4	0.97
Median	27.8	38.8		33.5	
Range	7.0–65.6	16.0–78.1		16.0–54.3	
Weight loss at study entry, percent[c]					
Mean	9.1	10.2	0.63	10.1	0.42
Median	7.7	8.1		8.6	
Range	5.0–15.0	5.0–26.5		5.0–26.5	
WAZ at study entry, z-score					
Mean	−0.87	−0.24	0.24	−0.32	0.33
Median	−0.55	+0.03		+0.03	
Range	−3.47 to 0.98	−1.92 to 1.09		−1.92 to 1.09	
BMI at study entry, z-score					
Mean	−0.97	−0.52	0.35	−0.52	0.37
Median	−0.91	−0.56		−0.56	
Range	−3.67 to +1.12	−1.72 to +1.00		−1.72 to +1.00	
Nutritional category at study entry[d]					
Underweight	4	0	0.10	0	0.10
Normal	9	12		10	
Overweight	0	0		0	

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BMI, body mass index; MA, megestrol acetate; PNET, peripheral neuroectodermal tumor; WAZ, weight-for-age z-score. [a]Baseline of the 12 eligible placebo subjects who were randomized. Two of these subjects were entirely non-compliant and had no follow-up data. [b]Baseline of the 10 placebo subjects who took the placebo intervention and had follow-up data. [c]Percentage weight loss at study entry, relative to previous maximal weight before study entry. [d]Based upon Children's Oncology Group nutritional category definitions [8] according to BMI percentile, weight for length percentile, and ideal body weight for height/length percentile.

(Fig. 2B). No significant difference in mean HAZ was observed between the two arms (-0.19 ± 0.12 vs. -0.03 ± 0.14; difference -0.16; 95%CI: -0.27 to -0.04, $P = 0.10$). Mean BMI-Z increased for the MA group ($+1.58 \pm 1.37$ vs. -0.29 ± 0.50; difference $+1.87$ in favor of MA; 95%CI: $+0.95$ to $+2.78$, $P = 0.006$) (Fig. 2C). Mean percent change in MUAC increased significantly for the MA group compared to placebo ($+17.5\% \pm 14.7\%$ vs. $-0.3\% \pm 5.5\%$, respectively; difference $+17.8\%$ in favor of MA; 95%CI: $+8.3\%$ to $+27.4\%$, $P = 0.01$). Mean percent change in TSF did not differ ($+37.7\% \pm 41.0\%$ vs. $-2.4\% \pm 28.2\%$; difference $+41.1\%$; 95%CI: $+3.4\%$ to 76.8%, $P = 0.34$). Compared to the highest pre-enrollment weight (between date of malignancy diagnosis and enrollment on-study), the end study weight (as a percent change) in the MA arm was significantly higher compared to placebo ($+9.3\% \pm 15.7\%$ vs. $-11.0\% \pm 9.4\%$, respectively; difference $+20.3\%$ in favor of MA; 95%CI: $+8.5\%$ to $+32.2\%$, $P = 0.018$).

Secondary Outcomes: Dose Modifications and Requirement to Initiate Tube Feeds or PN

Four of thirteen (30.8%) subjects on the MA arm required decreases in the prescribed volume due to excessive hunger (25% reduction in 2 subjects; 50% reduction in 2 subjects), compared to none of the subjects receiving placebo (Fisher's exact *P*-value = 0.10). Three of ten (30%) evaluable subjects receiving placebo, compared to 0/13 subjects receiving MA, met early stopping rules for excessive weight loss ($\geq$15%) and were withdrawn from the

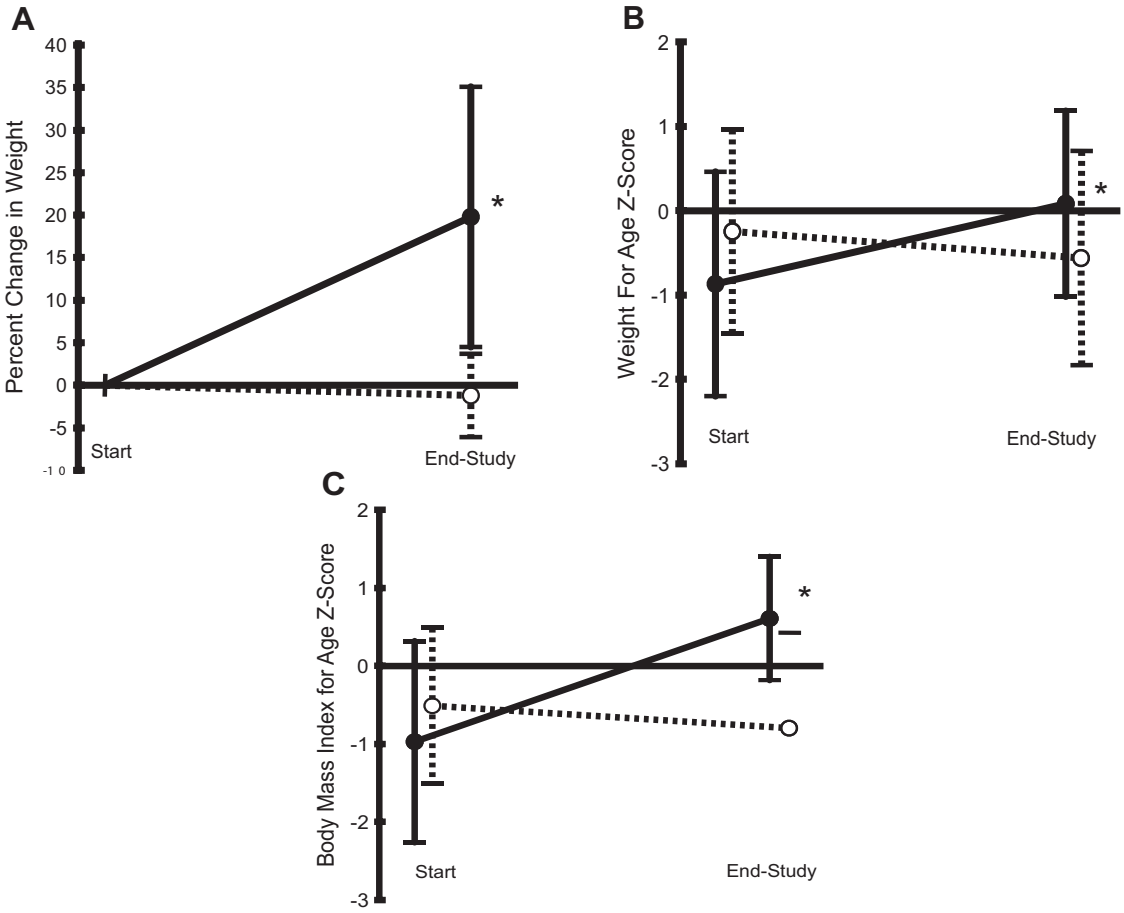

Fig. 2. Change in weight parameters from start to end of study. End-study reflects the actual time point when a participant was withdrawn from the study and final measurements were taken (either at the end of the 90 day study period, or earlier as described in the text). Solid line: MA arm; dashed line: placebo. Mean ± SD. (A) Change in percentage weight, $^{*}P = 0.003$. (B) Change in weight for age z-scores, $^{*}P = 0.002$. (C) Change in body mass index z-scores, $^{*}P = 0.006$.

study before 90 days to allow initiation of tube feeds or PN (Fischer's exact P-value = 0.07). None of the MA subjects received tube feeds or PN while on-study.

Secondary Outcomes: Body Composition by DXA

Nine MA subjects and five placebo subjects completed DXA scans at both the beginning and end of the study period, and were evaluable against age- and machine-adjusted normative z-scores (Table III) [21,22]. Analysis of pre- and post-DXA scans could not be performed for the remaining subjects (n = 4 at least one DXA scan not completed due to clinical illness; n = 4 subject too young, no available comparative age-adjusted z-scores; n = 1 results inaccurate due to patient movement). Mean change in %fat mass z-score over the duration of the study increased by +0.90 (range:

TABLE II. Summary of Changes in Weight and Anthropometric Parameters Between Megestrol Acetate and Placebo Arms From Beginning to End of Study Period

Parameter	Megestrol acetate (±SD)	Placebo (±SD)	Difference in favor of megestrol acetate (95% CI)	P-value
Mean percent weight change	+ 19.7% (±15.3%)	−1.2% (±4.9%)	+20.9% (+11.3% to +30.5%)	0.003
Mean change in WAZ	+ 1.00 (±0.79)	−0.18 (±0.34)	+ 1.18 (+0.67 to+1.70)	0.002
Mean change in BMI-Z	+ 1.58 (±1.37)	−0.29 (±0.50)	+ 1.87 (+0.95 to +2.78)	0.006
Mean percent change in MUAC	+ 17.5% (±14.7%)	−0.3% (±5.5%)	+ 17.8% (+8.3% to 27.4%)	0.01
Mean percent change in TSF	+37.7% (±41.0%)	−2.4% (±28.2%)	+41.4% (+3.4% to +76.8%)	0.34
Mean percent weight change at end of study compared to highest pre-enrollment weight	+9.3% (±15.7%)	−11.0% (±z9.4%)	+20.3% (+8.5% to +32.2%)	0.018

BMI-Z, body mass index-for-age z-score; CI, confidence interval; MUAC, mid-upper arm circumference; SD, standard deviation; TSF, triceps skinfold thickness; WAZ, weight-for-age z-score.

TABLE III. Changes in WAZ and Body Composition Z-Scores by Dual Energy X-Ray Absorptiometry for Individual Study Participants From Beginning to End of Study

Participant UIN	Change in WAZ	DXA machine	Change in % fat-mass z-score	Change in lean body mass z-score	Change in bone mineral content z-score
MA group (n = 9)					
1	+1.01	LP	+1.31	−0.50	−0.42
2	+0.99	LP	+0.48	+0.22	−0.55
3	+1.83	LP	+1.58	+0.73	−0.34
4	+0.40	LP	+0.41	+0.18	+0.43
5	+1.19	LP	+1.03	+1.33	+0.12
6	+0.20	H	+1.00	−0.60	−0.30
7	+1.17	H	+1.00	+0.80	0.00
8	+0.28	H	+1.10	−0.40	0.00
9	+0.34	H	+0.20	−1.20	−0.1
Placebo group (n = 5)					
10	+0.18	LP	+0.79	−0.43	−0.08
11	−0.35	LP	−0.59	−0.05	−0.73
12	−0.52	H	0.00	−0.20	−1.90
13	+0.27	H	0.00	+0.60	0.00
14	−0.32	H	−0.20	−0.30	−0.7

DXA, dual energy X-ray absorptiometry; H, hologic; LP, lunar prodigy; MA, megestrol acetate; UIN, unique identifying number; WAZ, weight-for-age z-score.

+0.20 to +1.58) for the MA group compared to 0.00 (range: −0.59 to +0.79) for the placebo group ($P = 0.058$). No difference in change in mean bone mineral content z-scores between groups was observed. Change in lean body mass z-scores were felt to not be directly comparable between the Lunar and Hologic machines due to differences in how the software calculates this variable between machines. Aggregate data for lean body mass is therefore not presented. Since the same DXA machine was used for each subject over time, however, descriptive analysis was possible to show changes within individual participants. Whereas all subjects receiving MA experienced increases in %fat mass, changes in lean body mass for the MA group were more variable. Four of nine MA subjects lost lean body mass (change in z-scores ranging between −0.4 and −1.2), 2/9 stayed relatively stable (+0.18 and +0.22), and 3/9 had increases in lean body mass (range: +0.73 to +1.33). Similar variability in lean body mass change was observed in the placebo group (Table III).

Toxicity

All thirteen (100%) of the MA participants developed at least one undetectable 8:00 AM cortisol level (<25 nmol/L) during the study period, compared to 1/10 receiving placebo (Fisher's exact *P*-value = 0.0001). In all MA cases, cortisol levels were undetectable by either the 2- or 4-week measurement, and except for two subjects, remained undetectable for the study duration. Two participants with undetectable cortisol levels were administered stress doses of hydrocortisone during severe illness events associated with their primary therapy. Both subjects were withdrawn early from the study and unblinded as per protocol. Both subjects were randomized to the MA arm. One subject with acute myelogenous leukemia developed cardiovascular compromise (hypotension and poor perfusion requiring inotropes) associated with a *Klebsiella pneumoniae* bacteremia. Adrenal suppression from MA was attributed as a severe toxicity and probable contributor to the hypotension. A second subject developed febrile neutropenia and neutropenic enterocolitis (but no cardiovascular compromise) following high-dose chemotherapy with autologous stem cell transplant. This subject was administered stress-dose hydrocortisone at the attending physician's discretion because of known low 8:00 AM cortisol levels. MA was felt not to be a contributor to the neutropenic enterocolitis or febrile neutropenia episode. Table IV describes the toxicity profile of subjects.

DISCUSSION

This randomized trial using a double-blind placebo-controlled study design demonstrates that MA results in significant increases in weight (both as a percentage weight gain and increase in WAZ) in pediatric oncology patients with weight loss due to cancer and/or

TABLE IV. Toxicities of Study Participants

Toxicity	MA arm (n = 13)	Placebo arm (n = 10)
Undetectable AM Cortisol	13	1
Clinically-relevant adrenal suppression (mild)	2	0
Clinically-relevant adrenal suppression (severe)	2	0
Hyperglycemia (asymptomatic, no glucosuria)	1	1
Hyperglycemia (symptomatic, polyuria, polydipsia, glucosuria)	0	0
Moodiness/Irritability (moderate)	3	3
Depression (mild/moderate)	2	2
Headaches	2	2
Yellow-stained teeth	1	0
Thromboembolism	0	0

MA, megestrol acetate.

cancer treatment. Our decision to use ≥5% weight loss as a major eligibility criterion, along with percent weight-change as the primary outcome of response, was strictly practical. A recent survey of children's cancer centers demonstrated no consistent approach to nutritional assessments across institutions [23]; the only marker of nutrition measured 100% of the time, was weight. By comparison, anthropometric measures (TSF and MUAC), which are better markers of nutritional status [24] but are more time consuming and require training and equipment to measure, were performed by only 5% of centers. We suspect this reflects real-life challenges that prevent detailed nutritional assessment in the clinical setting (time constraints, lack of expertise, equipment, and required personnel). Monitoring weight as a percent change from baseline offers an easily measurable, albeit imperfect screen for anorexia–cachexia syndrome [8]. Despite these limitations, change in weight remains the marker most clinicians still use to guide nutritional assessment and intervention.

Although we did not monitor dietary intake, the only subjects requiring dose reductions for excessive hunger were in the MA group. Given the significant increases in weight for the MA but not placebo group, we conclude weight gain could only have occurred through appetite stimulation and increased caloric intake from MA. Another secondary objective of this study was to determine if MA could prevent ongoing weight loss during therapy, so as to prevent initiation of tube feeding or PN. Although not statistically different (likely underpowered to show a difference), the only participants to meet our stopping rule for tube feeds or PN due to ongoing weight loss were in the placebo group.

It is important to emphasize that improvement in appetite and subsequent weight gain is different than concluding MA improves nutrition or ameliorates malnutrition. Assessment of nutritional status in pediatric oncology patients is complex, and firm criteria defining malnutrition are not universally applied [25]. Current Children's Oncology Group guidelines define underweight as a BMI <5th percentile, weight for length <10th percentile, or ideal-body weight <90th percentile, and emphasize that weight loss may not be a universal sign of malnutrition [8]. Using these criteria, 9/13 (MA) and 12/12 (placebo) subjects would have still been considered normal weight upon entry to this study, despite having lost ≥5% weight from their baseline (and according to these same guidelines, would have been eligible for either tube feeds or PN).

As a secondary objective, we describe the effect of MA on markers of nutritional status and malnutrition. BMI is often used as a marker of nutritional status, including in children with cancer [8], but interpretation may be uncertain in young infants and children. Excluding the one MA subject under 24 months of age, we were able to show statistically significant increases in BMI z-scores for MA over placebo. Compared to BMI, arm anthropometry may be a more sensitive marker of malnutrition in pediatric oncology patients [26]. MUAC correlates with lean body mass in children with cancer [24]. Our results demonstrate significant increases in MUAC with MA, suggesting a possible shift towards improved muscle mass. Although trained dieticians performed the anthropometrics in our study, we suggest caution in over-interpretation of this finding given we were only able to describe MUAC as a percent change over time (as opposed to a normalized z-score, which is not available for individuals >145 cm) and we cannot exclude some variability in measurement. This observation requires further investigation in future clinical trials. By contrast, body composition by DXA scanning suggested quite variable changes in lean body mass within the MA group, with four MA subjects actually losing lean body mass and two subjects experiencing relatively stable lean body mass, all while accruing fat and gaining weight during the study period. Furthermore, mean bone mineral content, which correlates with lean body mass [27], did not change for the entire MA group compared to placebo. Eight of nine MA subjects also appeared to have disproportionately greater increases in %fat mass compared to lean body mass, suggesting that when diet is not controlled and caloric intake not monitored (as in our study), MA may preferentially promote energy storage as fat. Increase in adipose tissue has previously been reported as the reason for weight gain in adults receiving MA for cancer-associated anorexia–cachexia [28], supporting the notion that similar may occur in children. Our body composition findings should be considered hypothesis generating rather than firm conclusions, as the number of subjects with both baseline and end of study DXA scans was small. Nonetheless, it is concerning that some MA participants exhibited a disproportionate amount of weight gain from fat accrual without similar increases in lean body mass. Increased fat deposition has been associated with heightened risk for developing metabolic syndrome in children with cancer [29], whereas severe muscle depletion (sarcopenia) is predictive of shorter time to tumor progression and dose-limiting toxicities in oncology patients [30].

Overall MA was assessed as safe, although adrenal suppression is a major potential toxicity, both in our study and others [31–33]. We do not view this as an absolute contraindication to MA use in children, but would recommend frequent monitoring of 8:00 AM cortisol levels and initiation of stress doses of hydrocortisone for patients exhibiting cardiovascular compromise while on MA.

The major strengths of this trial are the study design and practical outcome measures of response. We have demonstrated that MA increases weight compared to placebo in children with weight loss due to cancer and/or cancer therapy. We suggest caution in the widespread adoption of MA for cancer-associated anorexia–cachexia in children at this point in time, however, until further study into the effects on nutritional status are clearer. Future trials with sufficient power to determine effects on nutritional status are needed. Such trials should focus on controlling nutritional intake in a manner that promotes optimal quality and quantity of weight gain. Finally, further study into new appetite stimulating agents with less potential for adverse events are needed.

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