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The effect of cyproheptadine hydrochloride (Periactin®) and megestrol acetate (Megace®) on weight in children with cancer/ treatment-related cachexia

Marisa Couluris, D.O.[1], **Jennifer L.R. Mayer, M.D.**[1], **David R. Freyer, D.O., M.S.**[2], **Eric Sandler, M.D.**[3], **Ping Xu, M.P.H.**[1], and **Jeffrey P. Krischer, Ph.D.**[1]

[1] University of South Florida, Department of Pediatrics, Tampa, FL

[2] Childrens Center for Cancer and Blood Disorders, Childrens Hospital Los Angeles and University of Southern California Keck School of Medicine, Los Angeles, CA

[3] Nemours Children's Clinic, Jacksonville, FL

Abstract

Background—Children with cancer frequently have associated cachexia and malnutrition. Failure to thrive affects nearly 40% of oncology patients with advanced or progressive disease. Malnutrition can erode quality of life and adversely impact disease prognosis. Appetite stimulation and increased food intake is one approach to combat cancer-related cachexia.

Materials and Methods—Cyproheptadine hydrochloride (CH), an appetite stimulant, was administered to children with cancer-associated cachexia to prevent further weight loss. All participants started CH and were evaluated for response after four weeks. Efficacy of megestrol acetate (MA) was evaluated in patients who did not respond to CH. Medical evaluation, weight measurements, prealbumin and serum leptin levels were preformed at follow-up visits.

Results—Seventy patients were enrolled. Of the 66 evaluable patients, 50 demonstrated a response to CH (average weight gain 2.6kg and mean weight-for-age z-score change of 0.35, p=0.001). Seven of the 16 non-responders received MA. Six patients completed four weeks of MA, 5 responded (average weight gain of 2.5kg). The most commonly reported side effect of CH was drowsiness. One patient on MA developed low cortisol levels and hyperlipidemia.

Conclusions—This study demonstrates that CH is a safe and effective way to promote weight gain in children with cancer/treatment-related cachexia.

Keywords

cancer; weight loss; wasting; weight gain; appetite stimulant

Introduction

Cachexia is a frequent complication in patients with cancer. It affects as many as 80% of adult cancer patients and up to 40% of pediatric oncology patients with advanced or

Additional correspondence and request for reprint information: Marisa Couluris, University of South Florida, 3650 Spectrum Blvd; Suite 100, Tampa, Florida 33612; Phone: (813) 396-9547; Fax: (813) 910-5947; Marisa.Couluris@epi.usf.edu.

Additional participating institutions include the Children's Oncology Group, Arcadia, California (Gregory H. Reaman, M.D.); Scott & White CCOP, Temple, Texas (Lucas Wong, M.D.); University of Florida Pediatric, Shands Cancer Center, Gainesville, Florida; Bay Area Tumor Institute CCOP, Oakland, California (James Feusner, M.D.); Florida Pediatric CCOP, Tampa, Florida (James L. Talbert, M.D.); Medical College of Georgia MBCCOP, Augusta, Georgia (Anand P. Jillella, M.D.).

progressive disease.[1–3] Cachexia is a direct result of an imbalance between excessive energy expenditure and nutritional intake. Patients with metastatic and progressive disease are at greater risk for cachexia, thought to be due to tumor-secreted anorexins, host-derived tumor necrosis factor, interleukin-1 and interleukin-6.[4, 5] Cancer-related treatments are also instrumental in the development of cachexia. Nausea, vomiting, anorexia, early satiety and changes in taste perception are frequent side effects of radiation and chemotherapy. Acquired food aversions contribute to the problem, as well.[3] Depending upon the severity of the cachexia, clinical manifestations may vary. Weight loss, anorexia, aberrant carbohydrate metabolism (decreased glucose tolerance, increased glucose synthesis, insulin resistance, increased Cori cycle activity), skin and skeletal muscle atrophy, hypoalbuminemia, hyperlipidemia, anergy, and asthenia have all been observed in patients with cachexia.[3, 5] Malnourished children are much more susceptible to infectious complications and delayed wound healing due to cachexia-induced abnormalities in cell mediated immunity.[2, 6, 7] Pollack and colleagues have demonstrated that cachectic children are often physiologically unstable, require more therapeutic interventions and have a higher mortality rate than non-cachectic children.[8] The higher mortality rate is likely related to the increased toxicity of chemotherapeutic agents in malnourished patients.[9–11] In addition, cachexia profoundly impacts the psychological and emotional health of affected children. Coates *et. al.*, demonstrated that severely malnourished children often lack interest in play activities, have a decreased sense of well-being, and are less able to cope with disease-related treatments.[2]

Traditionally, cancer-associated cachexia in children has been treated with oral supplements, tube feedings and parenteral support.[3] While these methods may be effective in certain patients, they also have significant disadvantages. Oral supplements are commonly unpalatable to children and require large volumes to be effective. Nasogastric tube feedings cause nasal irritation and are cosmetically unappealing. Gastric tube feedings are contraindicated in some immunocompromised patients, require surgical placement, and are refused due to their appearance. Parenteral nutrition has been associated with catheter-related infectious complications, high cost, and possible stimulation of tumor growth.[5, 12–14] A preferable method to treat cancer-associated cachexia in children is to stimulate their appetite and increase their oral food intake. There are numerous studies in the adult oncology literature supporting the use of appetite stimulants such as megestrol acetate (MA) and cyproheptadine hydrochloride (CH) to promote weight gain.[5, 12, 15–18] These agents are also suited for use in children because of their low toxicity profile and palatable oral suspensions, when needed.

Cyproheptadine hydrochloride is a serotonin and histamine antagonist approved by the FDA for use in children for allergic rhinitis, allergic conjunctivitis, urticaria, dermatographism and mild angioedema. Unexplained weight gain has been observed in patients taking CH. Previous studies have demonstrated that this drug is an effective appetite stimulant in children with asthma, failure to thrive, short stature, and anorexia nervosa.[19–25] The current study is the first to report the use of CH for the management of pediatric cancer/treatment-related cachexia.

Megestrol acetate is a synthetic, antineoplastic, progestational agent with well-documented appetite stimulation and weight gain side effects. FDA-approved for AIDS-related cachexia, MA has also been extensively studied in adult cancer cachexia.[26–31] Reports in the pediatric literature demonstrate that MA promotes weight gain and improves nutritional status in patients with cystic fibrosis, AIDS and malignant solid tumors,[32–35] but its use can be complicated by potentially life-threatening adrenal suppression.[36, 37]

To evaluate nutritional status we measured surrogate markers including serum prealbumin and leptin levels at baseline and after four weeks of study agent. To date, there is no

consensus regarding which of the markers are most reliable measures of nutritional status; but, prealbumin is considered a sensitive marker of protein status in pediatric cancer patients.[6, 38, 39] Serum leptin levels are considered markers of body fat content.[40] They are associated with adipocyte production and have been found to correlate with body mass index in patients with and without cancer.[41–44]

Materials and Methods

Patient Population

Pediatric patients between the ages of 2–20 years of age with the diagnosis of cachexia secondary to cancer or cancer treatment-related therapy were eligible for this open-label sequential phase II trial. A placebo control was not utilized for this study due to the characteristics of our patient population. Our experience has been that clinicians were not willing to randomize their cachectic patients to a placebo-controlled trial, thus impacting study feasibility. More importantly, since documented cachexia was required for study entry, we thought it unethical to administer four weeks of a placebo in children who were already compromised. Cancer/treatment-related cachexia was defined as a documented history of weight loss of at least 5%, drop in growth rate two or more percentile ranks on standard growth charts, or a weight for height less than the tenth percentile on standard growth charts. Patients with newly diagnosed or relapsed cancer who were receiving active or palliative therapy, or who had completed therapy within eight weeks prior to study registration, were eligible. Exclusion criteria included patients taking appetite stimulating medications within three weeks of enrollment, receiving corticosteroids for more than seven days in the four week period, or receiving parenteral nutrition or tube feeding within one week of starting this protocol.

Treatment

Eligible patients were started on CH at 0.25 mg/kg/day orally in two divided doses, not to exceed 20mg/kg/day based on the recommended pediatric dose per the product insert.[45] This dose is consistent with the dose of CH used in previous pediatric studies of CH as an appetite stimulant.[45–47] Evaluation at the time of study enrollment and after four weeks of therapy included a medical evaluation, height, weight and blood pressure measurements, physical examination, serum leptin levels and serum prealbumin levels. Response to CH was evaluated at the end of study week four. Stable or increased weight was considered a treatment response. Stable weight was defined as an unchanged weight or a weight loss of less than one percentile. For patients who responded to CH, the decision to continue drug therapy beyond the first four weeks or discontinue it was made by the treating physician. A final study evaluation for patients who responded to CH was completed at week eight. Patients who exhibited no response to CH, defined as additional weight loss greater than or equal to one percentile, at the four week study visit, were eligible for a four week trial of MA 10 mg/kg/day in a single daily oral dose. Patients on MA had additional testing including serum glucose, morning cortisol level, lipid profile, and a testosterone level for males greater than 10 years old or an estradiol level for females greater than 10 years of age. These additional laboratory evaluations were important due to the potential for MA to induce hyperglycemia, adrenal suppression, sex hormone dysregulation, and elevated cholesterol and triglyceride levels. These evaluations were repeated after four weeks of MA and at the final study visit (study week 12). Stable or increased weight after four weeks of MA was considered a treatment response. For patients who responded to MA, the decision to continue MA therapy beyond four weeks or discontinue it was made by the treating physician. A final study evaluation was completed on week 12. All patients completed daily logs to document study agent intake and adverse events. Logs were reviewed at clinic visits to monitor study agent adherence and adverse events. Overall compliance to study agent

consumption was high and less than 7% of scheduled doses were missed. Compliance did not differ significantly between responders and non-responders. Adverse events were graded using the CTC Version 2.0 and reported to the Research Base.

Statistical Analysis

Data were analyzed using an intent-to-treat analysis. Paired t-tests were used to compare pre versus post treatment changes in weight, prealbumin and leptin levels. Leptin levels were not normally distributed and were log transformed for analysis. Sign test was used to compare pre-versus post-treatment change in weight-for-age z-score. The correlation between treatment-associated changes in weight and changes in surrogate markers (prealbumin and leptin levels), were obtained by Spearman's non-parametric correlation method. At the conclusion of the intervention, the response rate and non-response rate for CH were calculated and 95% exact confidence intervals were obtained. Pearson's chi square or Fisher's exact test was used to compare the proportions among responders and non-responders within defined age groups depending on the cell size. Non-parametric Wilcoxon rank sum test was used to compare the continuous variables between two groups. Kruskal-Wallis test was used for the multiple group comparisons. Tests were two-sided at 0.05 significance levels. The analysis was implemented in SAS version 9.

Results

Seventy patients from twenty institutions were enrolled and underwent baseline testing prior to initiation of CH therapy. Patient demographic and clinical data are provided in Table 1. Sixty-six patients had a documented history of weight loss greater than 5%. Two patients had a drop in growth rate greater than two percentiles and two patients had a weight for height less than the tenth percentile. There were 30 females and 40 males with a median age of 11.7 years (range, 3.2–19.4 years). The study population included patients with multiple types and stages of both relapsed and newly diagnosed cancer. Of the 70 enrolled patients, 66 were evaluable for response to CH therapy. The four non-evaluable patients included one patient who was noncompliant with the protocol regimen; two patients who withdrew consent within a few days of starting CH due to CH-related drowsiness; and one patient who was withdrawn within the first week due to cancer-related symptoms that impaired ability to take oral medication.

Fifty patients responded to CH (response rate of 76%, 95% CI: 64%–85%), and 16 patients were classified as non-responders (failure rate of 24%). Of the 50 responders, 48 patients gained weight and two patients had stable weights. There were no significant differences in baseline characteristics observed between responders and non-responders. The mean weight gain for the patients who responded to CH was 2.6 kg (range −0.1–10 kg, 95% CI: 1.93–3.27). Weight-for-age z-scores were used to compare a patient's weight to the average weight of a healthy child of the same age. The average change in z-score for the CH responders was 0.35 (range −0.09–1.89, 95% CI: 0.25–0.45).

Table 2 documents weight, weight–for-age z-scores, and prealbumin and leptin levels for responders to CH at baseline and after four weeks of therapy. Of the 50 responders, 40 patient samples for serum prealbumin collected at baseline and the four week follow-up visit. The baseline mean was 21.8 mg/dL and at four weeks, the mean increased to 23.94 mg/dL (p-value =0.25). The average change in prealbumin levels was 2.14 mg/dL (95%CI: −1.41 – 5.68). Serum leptin levels were evaluated for 32 patients of the 50 responders both at baseline and at the four week follow-up visit. The mean baseline was 1.19 mg/dL and increased to a mean of 1.83 mg/dL after four weeks of CH (p-value = 0.0004). The average change in leptin levels was 0.64 mg/dL(95%CI: 0.32 – 0.96). Sixteen patients failed to

respond to CH, with a mean change from baseline weight of -1.46 kg (range, −0.3 – −3.6 kg) and a mean change in weight-for-age z-score of −0.28 (range, −0.05 – −0.65).

To evaluate response based on age, patients were stratified into three groups at enrollment. Group 1 included patients less than nine years of age, group 2 included patients 9 through 13 years of age and group 3 included patients greater than 13 years old. Approximately 26% of patients were in group 1 and 38% and 36% were in groups 2 and 3, respectively. The proportion of responders and non-responders among the three strata did not differ significantly. The proportion of patients who demonstrated a response in the three strata were 71%, 76% and 79%, respectively (p-value = 0.82). There was a significant absolute weight change demonstrated among the three groups (Table 3). Responders in groups 2 and 3, representing patients greater than or equal to nine years old, gained significantly more weight than those in group 1 (p=0.003). The change in weight-for-age z-score also demonstrated a similar pattern, but was not statistically significant.

Interestingly, a significantly different response rate to CH was demonstrated when the response in patients with hematological malignancies (leukemia/lymphoma) was compared to non-hematological malignancies (p=0.04). A total of 25 patients with diagnosed hematologic malignancies were enrolled onto study. Among them, 23 were evaluated for response to CH at the follow-up visit. The response rate was 91.30% among these patients (21 out of 23). The response rate in patients with non-hematologic malignancies was 67.44% (29 out of 43). While the response rates differed significantly, the actual change in weight and weight-for-age z-scores did not differ significantly between patients with hematological compared to non-hematological malignancies. The mean weight change for hematological versus non-hematological malignancies was 2.90 (±2.54) and 2.39 (±2.26), respectively p= 0.46. The mean change in weight-for-age z-score for hematological versus non-hematological malignancies was 0.31 (±0.25) and 0.38(±.41), respectively p=0.95.

There were no serious adverse events reported during the study. The most common adverse events reported by patients taking CH included drowsiness, headache, insomnia, and dry mouth. These events were not unexpected in light of CH's mechanism of action as a histamine antagonist. Three patients were not able to continue therapy due to drowsiness. Two were not evaluable for response. There were no unexpected adverse events documented in patients taking CH.

Of the 16 patients who failed to respond to CH, 7 proceeded to MA treatment per protocol. One patient with no reported side effects was taken off study at the discretion of the treating physician. A total of 6 patients completed the four week trial of MA and 5 responded to therapy. The average weight gain was 2.5 kg (range 0.6–5.9 kg). Asymptomatic hypocortisolemia and hyperlipidemia were observed in one patient. There were no side effects associated with MA that required study withdrawal.

Discussion

Cachexia is a common but challenging problem in children with cancer. Malnutrition adversely impacts a patient's quality of life and his/her ability to tolerate aggressive therapeutic interventions. Appetite stimulation and increased oral food intake are physiologically preferable approaches for inducing weight gain. In this study, we demonstrated for the first time that CH can evoke a statistically significant increase in body weight among cachectic pediatric oncology patients.

Review of the literature reveals that CH is highly efficacious in many clinical conditions associated with weight loss, including asthma, anorexia nervosa, tuberculosis, and cystic fibrosis.[19, 20, 23, 24, 48–50] Lavenstein *et. al.,* observed a >200% weight gain with CH

therapy in children with asthma versus those on placebo for 15 weeks.[19] Homnick and colleagues demonstrated that patients with cystic fibrosis had a mean increase of 3.45 kg compared to 1.1 kg in the placebo group after taking CH for 12 weeks to nine months.[49, 50] Recently CH has been studied in patients with ADHD and stimulant-induced weight loss. All 21 patients on CH for two weeks gained a mean of 2.2 kg compared to a 2.1 kg weight loss in the placebo group.[51]

Our study is the first to rigorously investigate CH-induced weight gain in children with cancer-associated cachexia. Our finding of a mean weight gain of 2.6 kg in 50 CH-treated patients is consistent with the observations of other pediatric CH trials.[49–51] Likewise, our study duration of four weeks compares favorably with other reported studies of children receiving CH for one week to nine months.[19, 49–51]

In our study, CH at a dose of 0.25 mg/kg/day was associated with a statistically significant weight gain in approximately 76% of evaluable patients. Serum prealbumin and leptin levels were utilized as surrogate markers for weight gain and to investigate protein and fat deposition induced by the study agent. The change in serum prealbumin levels at four weeks was not statistically significant in patients treated with CH. In contrast, serum leptin did increase significantly in our patients treated with CH. Leptin is a protein hormone produced by adipocytes and involved in the maintenance of stable bodymass.[40] Cancer cachexia has been shown to be associated with reduced or normal levels of serum leptin, likely due to either the lack of new deposition or overall loss of adipose tissue, respectively.[52, 53] While we did not measure body-mass index (BMI) in this study, literature supports a correlation between an increase in serum leptin levels and increases in BMI.[41, 42]

An age-dependent response to CH was demonstrated in this study population. Although the proportion of responders did not differ among the three age groups, patients in the two older groups, collectively those children greater than nine years of age, gained more weight than younger patients. This may be partly explained by the increase in weight velocity commonly observed during puberty.

Another interesting finding of our study was the difference observed in response rate to CH when comparing patients with hematologic malignancies and solid tumors. While a significantly higher proportion of patients with hematologic malignancies responded to CH, they did not gain more weight than patients with solid tumors. Corticosteroids are commonly prescribed for patients with hematologic malignancies, which could be a confounding factor in studies measuring weight change; however, this study excluded patients who were expected to receive corticosteroids for more than seven days during the 4-week treatment period as part of therapy. This finding suggests that while patients with hematologic malignancies may not be at highest risk for cachexia, those who do develop cachexia as a consequence of their malignancy or treatment will respond favorably to appetite stimulation with CH.

Sixteen of our patients failed to respond to CH therapy and slightly less than half of these non-responders received MA per protocol. The majority of the patients who completed four weeks of MA had weight gain comparable to that observed in the CH group (mean 2.5 kg vs. 2.6 kg, respectively). However, the MA sample size was too small in this study to draw any significant conclusions about the efficacy of MA in pediatric oncology patients.

The safety profile for CH was consistent with the published literature. CH was well tolerated with rare adverse events, all of which were related to its antihistaminic effects. Only three patients (5%) treated with CH had excessive somnolence requiring withdrawal from the study. According to the literature, this side effect is typically self-limiting and generally reported within the first few days of therapy in both pediatric and adult studies.[19, 24, 49]

Hypocortisolemia and hyperlipidemia were observed in a single patient receiving MA therapy, which are also known documented side effects seen in patients taking MA.

Potential limitations of this study are its lack of a placebo control group and the duration of the medication trial. The investigators felt that it was unethical to withhold treatment from an already cachectic and fragile population for the sole purpose of establishing a placebo group. The risks of cachexia out-weighed the benefits of improved research design. Our experience has also demonstrated that a placebo-controlled trial in this patient population is not feasible. Treating physicians are unwilling to randomize to placebo when patients already meet the criteria for cachexia. This study did not assess the duration of patient response to CH or the long term safety profile of this agent. These are both issues which will need to be addressed in future studies.

Conclusions

In summary, CH is a safe and effective appetite stimulant in pediatric patients with cancer-associated cachexia. Patients receiving daily oral CH experienced excellent weight gain during the first four weeks of therapy. The elevation of serum leptin levels in patients on CH suggests fat deposition as a possible mechanism of increased body mass and further studies are needed to evaluate the usefulness of leptin as an indicator of nutritional status. The most common side effects of this drug are drowsiness, headache, insomnia and dry mouth. MA is also an effective appetite stimulant, but due to its safety profile, may be more appropriate as second-line therapy. Additional studies of CH with longer follow-up and a larger study population are necessary. A standard of care for treatment of pediatric cancer-associated cachexia is needed. Future investigations to evaluate the clinical outcomes related to treatment of cachexia such as tolerance to chemotherapy, infection rates and quality of life are warranted. Likewise, the potential role of CH as a prophylactic agent for cancer cachexia remains to be investigated.

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References

1. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. Oct; 1980 69(4):491–497. [PubMed: 7424938]
2. Coates TD, Rickard KA, Grosfeld JL, Weetman RM. Nutritional support of children with neoplastic diseases. Surg Clin North Am. Dec; 1986 66(6):1197–1212. [PubMed: 3097847]
3. Norton, J.; Peter, J. Nutritional supportive care in principles and practices of pediatric oncology. Philadelphia, PA: Lippincott and Co; 1989.
4. Langstein HN, Norton JA. Mechanisms of cancer cachexia. Hematol Oncol Clin North Am. Feb; 1991 5(1):103–123. [PubMed: 2026566]
5. Nelson KA, Walsh D, Sheehan FA. The cancer anorexia-cachexia syndrome. J Clin Oncol. Jan; 1994 12(1):213–225. [PubMed: 8270980]
6. Yu LC, Kuvibidila S, Ducos R, Warrier RP. Nutritional status of children with leukemia. Med Pediatr Oncol. 1994; 22(2):73–77. [PubMed: 8259104]
7. Hanigan MJ, Walter GA. Nutritional support of the child with cancer. J Pediatr Oncol Nurs. Jul; 1992 9(3):110–118. [PubMed: 1497824]

8. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. JPEN J Parenter Enteral Nutr. May–Jun; 1985 9(3):309–313. [PubMed: 3925174]
9. Grossie VB Jr, Ho DH, Loo TL. Effect of malnutrition on methotrexate toxicity and tissue levels of dihydrofolate reductase in the rat. Cancer Treat Rep. Jan; 1982 66(1):85–89. [PubMed: 7053272]
10. Obama M, Cangir A, van Eys J. Nutritional status and anthracycline cardiotoxicity in children. South Med J. May; 1983 76(5):577–578. [PubMed: 6573781]
11. van Eys J. Nutrition in the treatment of cancer in children. J Am Coll Nutr. 1984; 3(2):159–168. [PubMed: 6432872]
12. Levine AS, Brennan MF, Ramu A, Fisher RI, Pizzo PA, Glaubiger DL. Controlled clinical trials of nutritional intervention as an adjunct to chemotherapy, with a comment on nutrition and drug resistance. Cancer Res. 1982; 42(2 Suppl):774s–781s. [PubMed: 6799196]
13. Popp MB, Kirkemo AK, Morrison SD, Brennan MF. Tumor and host carcass changes during total parenteral nutrition in an anorectic rat-tumor system. Ann Surg. Feb; 1984 199(2):205–210. [PubMed: 6421254]
14. Christensen ML, Hancock ML, Gattuso J, et al. Parenteral nutrition associated with increased infection rate in children with cancer. Cancer. Nov 1; 1993 72(9):2732–2738. [PubMed: 8402497]
15. Ottery FD. Supportive nutrition to prevent cachexia and improve quality of life. Semin Oncol. Apr; 1995 22(2 Suppl 3):98–111. [PubMed: 7740324]
16. Bruera E. Pharmacological treatment of cachexia: any progress? Support Care Cancer. Mar; 1998 6(2):109–113. [PubMed: 9540168]
17. Gagnon B, Bruera E. A review of the drug treatment of cachexia associated with cancer. Drugs. May; 1998 55(5):675–688. [PubMed: 9585863]
18. Mantovani G, Maccio A, Massa E, Madeddu C. Managing cancer-related anorexia/cachexia. Drugs. 2001; 61(4):499–514. [PubMed: 11324680]
19. Lavenstein AF, Dacaney EP, Lasagna L, Vanmetre TE. Effect of cyproheptadine on asthmatic children. Study of appetite, weight gain, and linear growth. JAMA. Jun 16.1962 180:912–916. [PubMed: 14462919]
20. Bergen SS Jr. Appetite Stimulating Properties of Cyproheptadine. Am J Dis Child. Sep.1964 108:270–273. [PubMed: 14168064]
21. Penfold JL. Effect of cyproheptadine and a multivitamin preparation on appetite stimulation, weight gain and linear growth. A clinical trial of 40 children. Med J Aust. Feb 6; 1971 1(6):307–310. [PubMed: 5546215]
22. Antoon, A.; Bode, H.; Crawford, J. Effect of cyproheptadine on growth in short, underweight children. [Abstract] The American Pediatric Society, Inc. and The Society for Pediatric Research: combined program and abstracts. Pediatr Res; Annual meeting. The San Francisco Hilton Hotel; San Francisco, California. May 17–19, 1973; Apr. 1973 p. 229-484.
23. Halmi KA, Goldberg SC. Cyproheptadine in anorexia nervosa [proceedings]. Psychopharmacol Bull. Apr; 1978 14(2):31–33. [PubMed: 349601]
24. Goldberg SC, Halmi KA, Eckert ED, Casper RC, Davis JM. Cyproheptadine in anorexia nervosa. Br J Psychiatry. Jan.1979 134:67–70. [PubMed: 367480]
25. Arisaka O, Shimura N, Nakayama Y, Yabuta K. Cyproheptadine and growth. Am J Dis Child. Sep; 1988 142(9):914–915. [PubMed: 3414615]
26. Tchekmedyian NS, Tait N, Moody M, Aisner J. High-dose megestrol acetate. A possible treatment for cachexia. Jama. Mar 6; 1987 257(9):1195–1198. [PubMed: 3806918]
27. Bruera E, Macmillan K, Kuehn N, Hanson J, MacDonald RN. A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status, and other symptoms in patients with advanced cancer. Cancer. Sep 15; 1990 66(6):1279–1282. [PubMed: 2205358]
28. Feliu J, Gonzalez-Baron M, Berrocal A, et al. Usefulness of megestrol acetate in cancer cachexia and anorexia. A placebo-controlled study. Am J Clin Oncol. Oct; 1992 15(5):436–440. [PubMed: 1524045]
29. Loprinzi CL, Michalak JC, Schaid DJ, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. J Clin Oncol. Apr; 1993 11(4):762–767. [PubMed: 8478668]

30. Oster MH, Enders SR, Samuels SJ, et al. Megestrol acetate in patients with AIDS and cachexia. Ann Intern Med. Sep 15; 1994 121(6):400–408. [PubMed: 8053613]

31. Megace Oral Suspension (Megestrol Acetate). NJ: Mead Johnson Oncology Products, A Bristol-Myers Squibb Company; 1995.

32. Brady MT, Koranyi KI, Hunkler JA. Megestrol acetate for treatment of anorexia associated with human immunodeficiency virus infection in children. Pediatr Infect Dis J. Aug; 1994 13(8):754–756. [PubMed: 7970985]

33. Azcona C, Castro L, Crespo E, Jimenez M, Sierrasesumaga L. Megestrol acetate therapy for anorexia and weight loss in children with malignant solid tumours. Aliment Pharmacol Ther. Aug; 1996 10(4):577–586. [PubMed: 8853762]

34. Nasr SZ, Hurwitz ME, Brown RW, Elghoroury M, Rosen D. Treatment of anorexia and weight loss with megestrol acetate in patients with cystic fibrosis. Pediatr Pulmonol. Nov; 1999 28(5): 380–382. [PubMed: 10536070]

35. Marchand V, Baker SS, Stark TJ, Baker RD. Randomized, double-blind, placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis. J Pediatr Gastroenterol Nutr. Sep; 2000 31(3):264–269. [PubMed: 10997370]

36. Stockheim JA, Daaboul JJ, Yogev R, Scully SP, Binns HJ, Chadwick EG. Adrenal suppression in children with the human immunodeficiency virus treated with megestrol acetate. J Pediatr. Mar; 1999 134(3):368–370. [PubMed: 10064680]

37. Azcona C, Sierrasesumaga L. Adrenal suppression in children with malignant solid tumors treated with megestrol acetate. J Pediatr. Jul; 2000 137(1):141–142. [PubMed: 10891840]

38. Prealbumin in Nutritional Care Consensus Group. Measurement of visceral protein status in assessing protein and energy malnutrition: standard of care. Nutrition. Mar-Apr; 1995 11(2):169–171. [PubMed: 7647483]

39. Elhasid R, Laor A, Lischinsky S, Postovsky S, Weyl Ben Arush M. Nutritional status of children with solid tumors. Cancer. Jul 1; 1999 86(1):119–125. [PubMed: 10391571]

40. Wauters M, Considine RV, Van Gaal LF. Human leptin: from an adipocyte hormone to an endocrine mediator. Eur J Endocrinol. Sep; 2000 143(3):293–311. [PubMed: 11022169]

41. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. Feb 1; 1996 334(5):292–295. [PubMed: 8532024]

42. Blum WF, Englaro P, Hanitsch S, et al. Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J Clin Endocrinol Metab. Sep; 1997 82(9):2904–2910. [PubMed: 9284717]

43. Argiles JM, Lopez-Soriano FJ. The role of cytokines in cancer cachexia. Med Res Rev. May; 1999 19(3):223–248. [PubMed: 10232651]

44. Mete R, Dylek Y, Algun E, et al. Relationship between leptin levels and body index in patients with haematologic malignancy. Turk J Haematol. 2001; 18(3):185–189.

45. Periactin [package insert]. Whitehouse Station, NJ: Merck & Co Inc; 2002.

46. Kaplowitz PB, Jennings S. Enhancement of linear growth and weight gain by cyproheptadine in children with hypopituitarism receiving growth hormone therapy. J Pediatr. Jan; 1987 110(1):140–143. [PubMed: 3794875]

47. Klein GL, Galant SP. A comparison of the antipruritic efficacy of hydroxyzine and cyproheptadine in children with atopic dermatitis. Ann Allergy. Mar; 1980 44(3):142–145. [PubMed: 7362092]

48. Rahman KM. Appetite stimulation and weight gain with cyproheptadine (periactin) in tuberculosis patients (double-blind clinical study). Med J Malaysia. Jun; 1975 29(4):270–274. [PubMed: 1105100]

49. Homnick DN, Homnick BD, Reeves AJ, Marks JH, Pimentel RS, Bonnema SK. Cyproheptadine is an effective appetite stimulant in cystic fibrosis. Pediatr Pulmonol. Aug; 2004 38(2):129–134. [PubMed: 15211696]

50. Homnick DN, Marks JH, Hare KL, Bonnema SK. Long-term trial of cyproheptadine as an appetite stimulant in cystic fibrosis. Pediatr Pulmonol. Sep; 2005 40(3):251–256. [PubMed: 16015665]

51. Daviss WB, Scott J. A chart review of cyproheptadine for stimulant-induced weight loss. J Child Adolesc Psychopharmacol. Spring;2004 14(1):65–73. [PubMed: 15142393]

52. Simons JP, Schols AM, Campfield LA, Wouters EF, Saris WH. Plasma concentration of total leptin and human lung-cancer-associated cachexia. Clin Sci (Lond). Sep; 1997 93(3):273–277. [PubMed: 9337643]

53. López-Soriano J, Carbó N, Tessitore L, López-Soriano F, Argilés J. Leptin and tumour growth in the rat. Int J Cancer. in press.

Table 1

Demographics and Baseline Clinical Data

Median Age (years)	11.7 (range, 3.2–19.4)
Gender	40 male, 30 female
Type of Cancer:	No. of patients
Leukemia	19
Sarcoma	15
Brain Tumor	13
Lymphoma	6
Hepatic tumor	1
Wilms' tumor	1
Neuroblastoma	1
Other	13
Stage of Cancer:	
I	2
II	6
III	4
IV	13
N/A	29
Unknown	16
New Diagnosis	62
Relapsed Disease	8

Table 2

Weight, weight for age z-scores, and serum markers for responders at baseline and after 4 weeks of CH

	N	CH Baseline	CH Week 4	p-value	Mean change after 4 weeks of CH	95%CI*
Weight (kg)	50	38.91+/−16.10	41.51+/−17.33	0.001	2.60	1.93 – 3.27
Weight-for-age z-score	50	−0.66+/−1.22	−0.31+/−1.17	0.001	0.35	0.25 – 0.45
Prealbumin Levels(mg/dL)	40	21.8 +/− 9.88	23.94 +/− 7.96	0.25	2.14	−1.41 — 5.68
Log Leptin Levels (mg/dL)	32	1.19 +/−1.23	1.83 +/−1.09	0.0004	0.64	0.32 – 0.96

*95% Confidence Intervals refer to the mean change values after 4 weeks of CH

Table 3

The weight and weight-for-age z-score changes by age group

Absolute Weight change (kg)	N	Median	Maximum	Minimum	p-value*
ALL subjects					
Group 1	17	0.4	4	−2.1	0.05
Group 2	25	1.4	7	−3.1	
Group 3	24	2.45	10	−3.6	
Responders					
Group 1	12	0.85	4	0	0.003
Group 2	19	1.7	7	0.2	
Group 3	19	3.6	10	−0.1	
Non-Responders					
Group 1	5	−0.7	−2.1	−0.3	0.14
Group 2	6	−0.95	−3.1	−0.5	
Group 3	5	−2.3	−3.6	−0.8	

Weight-for-Age z-score change	N	Median	Maximum	Minimum	p-value
ALL subjects					
Group 1	17	0.12	1.89	−0.65	0.29
Group 2	25	0.15	0.92	−0.37	
Group 3	24	0.25	1.02	−0.33	
Responders					
Group 1	12	0.23	1.89	−0.09	0.4
Group 2	19	0.25	0.93	−0.002	
Group 3	19	0.42	1.02	−0.05	
Non-Responders					

Weight-for-Age z-score change	N	Median	Maximum	Minimum	p-value
Group 1	5	−0.33	−0.24	−0.65	0.14
Group 2	6	−0.27	−0.38	−0.13	
Group 3	5	−0.23	−0.33	−0.05	

* p-value calculated by the Kruskal-Wallis test comparing Group 1, Group 2 and Group 3.