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Clinical Outcomes and Contributors to Weight Loss in a Cancer Cachexia Clinic

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Abstract

Background: Cancer cachexia is considered intractable, with few therapeutic options. Secondary nutrition impact symptoms (S-NIS) such as nausea may further contribute to weight loss by decreasing nutrient intake. In addition, treatable metabolic abnormalities such as hypogonadism, vitamin B12 deficiency, hypothyroidism, and hypoadrenalism could exacerbate anorexia and muscle wasting in patients with cancer cachexia. We determined the frequency and type of contributors to appetite and weight loss, and the effect of the cachexia clinic on clinical outcomes.

Methods: Review of 151 consecutive patients referred to a cachexia clinic. All received dietary counseling and exercise recommendations. Assessments included weight, body mass index (BMI), S-NIS, resting energy expenditure by indirect calorimetry, serum thyroid stimulating hormone (TSH), cortisol, total testosterone, and vitamin B12.

Results: Median weight loss in the 100 days before referral was 9% (4%–13%); median BMI at presentation was 20.8. Median number of S-NIS was 3 (2–4), most commonly treated by metoclopramide, laxatives, and antidepressants. Forty-one percent (24/59) of patients were hypermetabolic and 73% (52/71) of males hypogonadic, whereas hypoadrenalism (0/101, 0%), hypothyroidism (4/113, 4%), and low vitamin B12 (3/107, 3%) were uncommon. Poor appetite and weight loss before referral ($r = 0.18$, $p = 0.036$) were associated with increased S-NIS ($r = 0.22$, $p = 0.008$). Appetite improved ($p < 0.001$) and 31/92 (34%) of patients returning for a second visit gained weight.

Conclusions: Patients had a high frequency of multiple S-NIS, hypogonadism, and hypermetabolism. A combination of simple pharmacological and nonpharmacological interventions improved appetite significantly, and increased weight in one third of patients who were able to return for follow-up. Cachexia clinics are feasible and effective for many patients with advanced cancer.

Introduction

Nutritional concerns are important to patients with cancer and their families[1] and can contribute to profound psychosocial distress and decreased quality of life.[2] Cachexia is also an independent risk factor for decreased survival[3,4,5] and poor response to chemotherapy.[6]

The Cachexia Working Group states "cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass . . ."[7] Developing a consensus for the definition of cachexia is important so that outcome measures and inception points for future intervention trials may be standardized. Unfortunately, the role of symptoms[8] and other metabolic abnormalities such as vitamin or endocrine deficiencies in cancer cachexia are ill-defined, and not yet incorporated into any working definitions. Identifying these causes of secondary cachexia (SC) may be an important component of cachexia management because effective, inexpensive therapies are available for symptoms even though they often appear to be underused.[9] Some secondary nutrition impact symptoms (S-NIS) such as nausea, depression, and pain can decrease caloric intake and add a "starvation" component to the catabolic process typically associated with cachexia. In addition, potentially reversible metabolic abnormalities that are easily identified by laboratory tests thyroid stimulating hormone (TSH), serum vitamin B12, testosterone, and cortisol) may also decrease appetite and/or lean body mass.

There are preliminary studies in patients with cancer that describe the potential role of S-NIS and other causes of

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secondary cachexia on weight loss and quality of life. The presence of anorexia and severe weight loss independently predicts a higher symptom burden[10] and in newly diagnosed patients with gastrointestinal or lung cancer, S-NIS[11] are associated with weight loss. Moreover, a prospective longitudinal study of patients receiving chemotherapy found higher numbers of S-NIS correlated with a poorer quality of life[2] and in head and neck cancer patients, multiple S-NIS prior to treatment are associated with reduced dietary intake and functional capacity.[12] A low-cost intervention such as nutritional counseling in patients with head and neck cancer improves symptoms (e.g., dysguesia and nausea) as well as overall quality of life.[13] Among other possible contributors to secondary cachexia, low testosterone is very common and associated with fatigue and poor appetite in patients with cancer,[14] whereas hypothyroidism prevalence may be as high as 30% in patients treated with radiotherapy for head and neck cancer.[15]

At the University of Texas M. D. Anderson Cancer Center, we have established an interdisciplinary cachexia clinic specializing in management of weight loss and anorexia. In this study, we determined the frequency and type of contributors to weight loss and anorexia, their respective interventions, and the effect of the cachexia clinic on clinical outcomes

Materials and Methods

Data were collected from a retrospective chart review of 151 consecutive patients referred to our cachexia clinic by their primary oncologists because of weight loss and/or poor appetite from November 2005 to September 2008. All patients either had a history of weight loss $\geq 5\%$ and/or complained of poor appetite. The study was approved by the Institutional Review Board at M. D. Anderson Cancer Center with waiver of informed consent.

Baseline demographic data collected from the chart included age, gender, tumor site and stage, treatment status, baseline weight, body mass index (BMI), and prior treatment for weight loss. All patients received dietary counseling by a dietician and standard exercise recommendations. The patient-generated subjective global assessment of nutritional status (PG-SGA)[16] is the most commonly used tool in studies evaluating S-NIS. We did not use the entire PS-SGA for our clinic evaluation because some of the symptoms incorporated into the PG-SGA are already found in the Edmonton Symptom Assessment Scale (ESAS). Our S-NIS assessment was based on a combination of the ESAS and the remaining nutrition impact symptoms found in the PG-SGA. Besides avoiding redundancy, the ESAS also has the advantage of providing a numeric rating scale from zero to 10 that may be used for monitoring the change in intensity of individual symptoms over time. The frequency of S-NIS (nausea, depression, pain, dental problems, taste changes, mouth sores, odynophagia, dry mouth, dysphagia, early satiety, and constipation) as well as ESAS scores (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, dyspnea, and sleep) were obtained at each visit. Laboratory tests including serum vitamin B12, TSH, total testosterone, and serum cortisol were done at baseline. The frequency and type of pharmacological therapies for secondary cachexia (S-NIS, vitamin and hormone deficiencies) were reviewed. In addition, patients who met eligibility criteria were also enrolled into randomized controlled trials (RCTs) of pharmacological interventions for primary cachexia (thalidomide, melatonin, or mirtazapine).

Bedside indirect calorimetry (IC) was measured using the Med Gem (HealtheTech, Golden, CO) handheld device. IC determines a more accurate caloric goal because resting energy expenditure usually constitutes the bulk of caloric needs. Although the device is simple and noninvasive, patients are advised not to eat or exercise within 4 hours prior to their visit. The majority of our patients were unable to complete IC on their first visit because of time constraints and difficulties tolerating nasal clamping and breathing through the handheld device.

After the initial consultation, similar data were also recorded for patients on follow-up visits. The reasons for loss to follow-up were obtained from the patients' electronic records.

Statistical analysis

We summarized baseline demographics, symptom characteristics, and results using descriptive statistics, including medians, interquartile ranges, ranges, and frequencies. To standardize the weight changes before and after cachexia clinic consultation, we divided the difference in weight by the time interval between visits and multiplied by 100.

We used the Spearman test to determine the association among body weight changes, number of NIS symptoms, and anorexia. We also used the Statistical Package for the Social Sciences software (SPSS version 17.0, SPSS Inc., Chicago, IL).

Results

A total of 151 patients were referred to the cachexia clinic from November 2005 to September 2008. Their demographic information is illustrated in Table 1. The median age was 60 years and all patients except 2 had advanced cancer (defined as metastatic or locally recurrent). Almost all (97%) had solid tumors including gastrointestinal, respiratory, head and neck, genitourinary, and sarcomas. At the initial consultation, the median adjusted prior weight loss was 5.9 kg (9%) and the median BMI was normal.

The frequency of S-NIS, vitamin and endocrine deficiencies, and their respective interventions are reported in Tables 2 and 3. The median number of S-NIS contributing to weight loss was 3 (Q1–Q3, 2–4) and 15% of patients experienced ≥ 5 symptoms. The most common symptoms reported were early satiety (94/151, 62%), constipation (78/151, 52%), nausea or vomiting (67/151, 44%), and mood changes (63/151, 42%). A median of 2 (Q1–Q3, 1–3) interventions per patient were recommended by the clinic physician during initial visit. The most common therapeutic interventions were metoclopramide (74/94, 79%), both for early satiety and nausea, laxatives for constipation (68/78, 87%), antidepressants for mood disorders (51/63, 81%), and zinc for dysgeusia (20/42, 48%). Loss of appetite was rated the most severe of the symptoms assessed by the ESAS (median 7, Q1–Q3, 4–9)

Adrenal insufficiency (0/101, 0%), hypothyroidism (4/113, 4%), and vitamin B12 deficiency (3/107, 3%) were found infrequently (Table 3). No patients were identified with uncontrolled diabetes mellitus (fasting glucose > 200 mg/dL) or hypercalcemia (corrected calcium > 10.5 g/dL). The majority (52/71, 73%) of male patients had hypogonadism, that is, total testosterone levels < 240 ng/dL (8.36 nmol/L).

Table 1. Patient Characteristics ($N = 151$)

Age in years, median (range)	60 (19–86)
Female sex	56 (37)
Primary cancer site	
Gastrointestinal	58 (38%)
Respiratory	33 (22%)
Genitourinary	16 (11%)
Head and neck	15 (10%)
Other	29 (19%)
Stage IV disease	147 (97%)
Body Mass Index, median (Q1–Q3)	21 (19–24)
Adjusted weight loss over the preceding 100 days in kg, median (Q1–Q3)	5.9 (3.2–9)
Adjusted % weight loss over the preceding 100 days in kg, median (Q1–Q3)	9 (4.5–12.8)
Hypermetabolic state[a]	24 (41%)
Edmonton Symptom Assessment Scale	
Pain	3 (1–6)
Fatigue	5 (4–8)
Nausea	1 (0–3)
Depression	1 (0–4)
Anxiety	1 (0–4)
Drowsiness	2 (0–5)
Appetite	7 (4–9)
Well–being	5 (3–6)
Dyspnea	2 (0–4)
Sleep	4 (1–7)
Active cancer treatment	97 (64%)
On appetite stimulants prior to clinic referral (e.g., megestrol, corticosteroids, dronabinol)	(33%)
Albumin <3.5 g/dL	46 (35%)

[a]defined as measured resting energy expenditure by indirect calorimetry >110% predicted.

Numbers in parentheses are ranges unless specified as a percentage.

Twenty-five of sixty (42%) patients were hypermetabolic as measured by indirect calorimetry and defined as a resting energy expenditure > 110% of predicted (by Harris-Benedict equation).

We found a statistically significant improvement of appetite scores between the 2 visits (median 7/10 versus 5/10, $p = 0.001$) of those patients able to return for follow-up. The adjusted median weight loss over 100 days after clinic consultation was 3.6 kg (Q1–Q3, 1.2–8.8 kg) or 5% (Q1–Q3, 2.6%—13%) among the 92 patients with return visits and weight measurements. Thirty-one of 92 (34%) of these individuals experienced a weight increase, with an adjusted median gain of 5.6 kg (Q1—Q3, 2.7—10 kg).

Fifty-nine of 151 patients did not return for a second visit because of death or hospice referral within 30 days, development of severe intractable pain or delirium, noncompliance, or residing out of state.

Poor appetite at baseline (by ESAS) was associated with an increased number of S-NIS (Spearman correlation coefficient $r = 0.22$, $p = 0.008$). The number of S-NIS was in turn associated with a higher adjusted percent of weight loss prior to clinic visit ($r = 0.18$, $p = 0.036$).The adjusted weight loss at the follow-up visit was associated with poor appetite at baseline ($r = 0.22$, $p = 0.035$) but not the number of S-NIS.

Discussion

S-NIS and hypogonadism (males) were common in patients referred to our cachexia clinic and hypermetabolism was identified in more than one third of patients who were tested. Poor appetite was associated with a higher burden of S-NIS and improved significantly after simple nonpharmacological and pharmacological interventions. Thirty-four of patients able to have a follow-up second clinic visit gained weight.

The high burden of gastrointestinal (GI) symptoms in this study, (e.g., early satiety, taste changes, constipation, nausea, or vomiting) has been reported previously in patients with advanced cancer.[17] Even cancer patients with good performance status have a high incidence of GI symptoms, particularly abdominal fullness.[18] Most of our patients had a normal BMI (median 21) even though the median weight loss at referral (over a period of 100 days) was 9%. Our findings are comparable to those of another palliative care center that reported 71% of patients lost weight (30% with significant muscle mass reduction) in spite of a normal or increased BMI.[19] The rise in obesity and physical inactivity among the general population may result in precancer obesity that masks the loss of lean body mass, leading to a combination of "sarcopenic obesity" in many patients.[20]

More than half of patients had 3 or more S-NIS and received at least 2 therapeutic interventions for symptom control. Optimal S-NIS management could help maintain adequate caloric intake and complement any specific interventions for cancer cachexia. S-NIS are easily identified by patient questionnaires and can be managed with relatively inexpensive pharmacological interventions such as laxatives, metoclopramide, and analgesics. Nonpharmacological interventions such as dietary counseling and exercise recommendations were provided to all patients as standard of care. Hypogonadism was identified in 73% of males, but other causes of

Table 2. Prevalence of Secondary Nutritional Impact Symptoms and Their Treatment

Nutrition impact symptoms	*Number (%)*	*Corresponding interventions*	*Number (% treated among effected individuals)*
Early satiety	94 (62%)	Metoclopramide	74 (79%)
Constipation	78 (52%)	Laxatives	68 (87%)
Nausea or vomiting	67 (44%)	Antiemetics (mostly metoclopramide)	54 (81%)
Depressed mood	63 (42%)	Antidepressant (mostly mirtazapine)	51 (81%)
Dysgeusia	42 (28%)	Zinc supplement	20 (48%)
Dysphagia	21 (14%)	GI or speech therapy evaluation	5 (24%)
Dry mouth	14 (9%)	Artificial saliva	2 (14%)
Mucositis	11 (7%)	Opioids and topical mouthwash	3 (27%)
Dental pain	8 (5%)	Dental referral	2 (25%)

Table 3. Vitamin or Endocrine Abnormalities

Number of patients tested		*Number of patients treated*	
Hypogonadism* (testosterone <240 ng/dL)	52/71 (73%)	**Testosterone Replacement**	15/52 (29%)
Adrenal Insufficiency (cortisol <4 mcg/dL)**	0/101 (0%)	**Corticosteroids**	NA
Hypothyroidism (TSH >5.5 mU/L)	4/113 (4%)	**Thyroid Hormone Replacement**	4/4 (100%)
Vitamin B 12 deficiency (<211 pg/mL)	3/107 (3%)	**Vitamin B12 Replacement**	3/3 (100%)

*Males only, **morning cortisol level.

secondary cachexia such as hypothyroidism and vitamin B12 deficiencies were rarely found and adrenal insufficiency was not identified in any patients. Our review indicated many patients (33%) were already prescribed an appetite stimulant (megestrol, corticosteroids, and dronabinol) by their oncologists prior to referral, despite the potential for side effects[21] and/or inconsistent benefit[22] of these medications. Most of these appetite stimulants were either discontinued or tapered after the first clinic visit. Sixty of 151 (40%) patients were enrolled into studies of anticachexia agents (either melatonin or mirtazapine or thalidomide), suggesting that the cachexia clinic is an important source of patients for clinical trials targeting weight loss and fatigue at our institution.

The limitations of our study included its retrospective nature and incomplete data, particularly the laboratory tests for secondary cachexia and IC measurements. The small number of patients and limited follow-up are challenges common to studies of patients with advanced cancer and weight loss. Except for those patients enrolled in RCTs for cachexia, functional outcomes or muscle strength were not routinely measured in the clinic. Also, we could not assess the clinical impact of the therapeutic interventions in more than one third of our clinic patients because they were unable to attend a follow-up second visit (Table 4). Almost 30% of these patients died or were admitted to hospice within 30 days of their first clinic visit. Clearly, many patients had very advanced cancer, were referred late in their disease trajectory, and it is likely their cachexia could be defined as "refractory"[9] and unresponsive to intervention. Finally, vitamin D levels were not routinely evaluated in this study but deficiency may be common in patients with cancer and could potentially contribute to muscle weakness[23] in cachexia patients. Serum levels of vitamin D_2 are now routinely evaluated in our clinic.

The frequency of hypermetabolism (42%) is similar to that in a previous study of unselected cancer patients with solid tumors, attending an outpatient clinic (48%).[24] Hypermetabolism is most likely related to primary cancer cachexia because we did not identify any patients with uncontrolled hyperthyroidism. Given that more than one third of those assessed were hypermetabolic, the caloric needs of many cachectic patients may be underestimated without the aid of IC. Also, preliminary evidence suggests beta blockers may be an effective intervention for those patients who are hypermetabolic.[25] Because of time constraints, the assessments incorporated into our cachexia clinic such as IC may not be routinely used in palliative care clinics.

Table 4. Patients Not Returning for a Second Visit

Causes	*Number of patients*	*Percentage*
Died <30 days of referral	7	11.9
Unable to follow up (residence out of state)	7	11.9
Hospice <30 days of referral	10	16.9
Decline to follow up or Noncompliant	17	29.8
Developed other intractable symptoms (e.g., pain/delirium)	18	29.8
Total	59/151	

Further research is required to better determine the relative contributions of primary cachexia, S-NIS, and other secondary causes toward weight loss and functional decline in an individual patient. Interventions should be initiated early in the disease trajectory because patients may become refractory to therapy as their disease burden increases. In addition, future intervention studies for cancer cachexia that are done against the background of "best supportive care" should consider including, and defining, the specific management of S-NIS. An assessment of specific symptoms, laboratory markers (e.g., of inflammation), anabolic hormones such as testosterone, and resting energy expenditure could refine individualized patient profiles for comprehensive, multimodality cachexia therapy.

Conclusion

Patients presenting to a cachexia clinic had a high frequency of S-NIS, hypogonadism, hypermetabolism, and severe involuntary weight loss. A combination of simple, inexpensive pharmacological and nonpharmacological measures resulted in significant appetite improvement on follow-up, and weight gain in one third of patients. Although the assessments are more time consuming than in a typical palliative care clinic and some patients with advanced disease might be refractory to anticachexia therapy, our findings suggest cachexia clinics are feasible and effective for many patients with advanced cancer.

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Author Disclosure Statement

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