The Role of Thalidomide and Placebo for the Treatment of Cancer-Related Anorexia-Cachexia Symptoms: Results of a Double-Blind Placebo-Controlled Randomized Study

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Abstract

Objectives: To determine the effects of thalidomide and placebo on anorexia-cachexia and its related symptoms, body composition, resting metabolic rate, and serum cytokines and their receptors in patients with advanced cancer.

Methods: Included in the study were patients with advanced cancer with weight loss greater than 5% in 6 months and who reported anorexia, fatigue, and one of the following: anxiety, depression, or sleep disturbances. Patients on chemotherapy within 2 weeks prior or during the study were excluded from the study. Patients were randomly assigned to either 100 mg thalidomide or placebo once a day for 14 days. The Edmonton Symptom Assessment Scale (ESAS), Functional Assessment of Anorexia/Cachexia Therapy (FAACT), Functional Assessment of Cancer Illness Therapy (FACIT-F), Hospital Anxiety Depression Scale (HADS) Pittsburgh Sleep Quality Index (PSQI) were utilized, and in addition body composition, Resting Energy Expenditure (REE), and serum cytokine levels were assessed.

Results: Of the 31 patients entered in the study, 15 were assigned to the thalidomide group and 16 to the placebo group. However only 21/31 patients were able to complete the study. Compared with their baseline values, both the thalidomide and the placebo groups showed significant reduction in cytokines. Tumor necrosis factor (TNF)- α ($p=0.04$) and its receptors TNFR1 ($p=0.04$), TNFR2 ($p=0.04$), and interleukin (IL)-8 ($p=0.04$) were statistically significant in the thalidomide group. In the placebo group, TNF- α ($p=0.008$), TNFR1 ($p=0.005$), TNFR2 ($p=0.005$), IL-6 ($p=0.005$), IL-8 ($p=0.005$), and IL-10 ($p=0.005$) were statistically significant. However, improvement in these symptoms and cytokine levels were not significantly different in the thalidomide group compared with the placebo group. None of the patients withdrew from the study because of toxicity of either thalidomide or placebo.

Conclusions: Based on the poor accrual rate and attrition observed in this study, it is important that future research on thalidomide as a treatment for cancer-related anorexia-cachexia symptoms (ACS) in patients with advanced cancer use less stringent entry criteria and less exhaustive outcome measures.

Introduction

ANOREXIA-CACHEXIA is a serious and underestimated consequence of advanced cancer occurring in 60% to 80% of patients with advanced cancer.^{1,2} Anorexia-cachexia-related symptoms (ACS) are distressing and affect quality of life of both patients and their families.³ There are few effective treatments for ACS in patients with advanced cancer.⁴⁻⁶

Various treatments have been investigated for ACS; however, they were found to be of limited efficacy in improving ACS.^{2,5,7} There has been renewed interest in the use of thalidomide for ACS.⁷ This interest is based on previous studies using thalidomide for the treatment of acquired immunodeficiency syndrome (AIDS)-associated cachexia⁸ and the effects of thalidomide in modulating the release of cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-10.⁹ It acts

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on the inflammatory pathways that contribute to the pathophysiology of ACS.¹⁰⁻¹²

In previous studies, administration of thalidomide (100–200 mg/day) in patients with cancer-related cachexia was found to be safe and led to significant reduction of symptoms of fatigue, chronic nausea, and weight loss, and improvement in appetite and sense of well-being.^{8,13} However, there are limited placebo-controlled studies of thalidomide for ACS using validated assessment tools in patients with advanced cancer who are not being actively treated with chemotherapy; likewise, the effects of the drug on serum cytokine levels have received little attention.^{14,15} The purpose of this study was to determine the effects of thalidomide and placebo on ACS, body composition, resting metabolic rate, and serum cytokines.

Methods

The University of Texas M.D. Anderson Cancer Center institutional review board approved this protocol, and all participants provided written informed consent.

Participants

Patients with advanced cancer with weight loss greater than 5% within 6 months who reported anorexia, fatigue, and one of the following: anxiety, depression, or sleep disturbances ($\geq 3/10$) during the preceding 24 hours were included in the study. The rationale for inclusion of fatigue, anxiety, depression, and sleep disturbance is because patients with advanced cancer with weight loss often experience a cluster of these symptoms and thalidomide by its action on common inflammatory cytokines that are associated with these symptoms may alleviate this cachexia symptom cluster.^{11,16,17}

Other important inclusion criteria were as follows: no clinical evidence of cognitive failure; negative serum pregnancy test; no concurrent use of steroids; and no history of AIDS, systemic lupus erythematosus, or renal failure. Patients were excluded if their absolute neutrophil count at the time of study enrollment was $\leq 750/\text{mm}^3$, or if they had started on chemo-

TABLE 1. PATIENT CHARACTERISTICS

Patient characteristics	N=31	%
Median age	60 years (range 24–81)	
Male gender	19	59
Race		
African American	4	13
Caucasian	25	78
Asian	0	0
Hispanic	3	9
Other	0	0
Performance status(ECOG)		
0	0	0
1	7	21
2	13	41
3	12	38
4	0	0
Diagnosis		
Head and neck lung cancer	5	15
Breast	2	6
Melanoma	2	6
Gynecology	4	12
Gastrointestinal	5	16
Genitourinary	5	16
Others	9	29

ECOG, Eastern Cooperative Oncology Group.

therapy or targeted or hormone therapies in the 2 weeks prior to the initiation of the study or after initiation of the study.

Intervention

Patients were randomly assigned to receive either 100 mg thalidomide orally, once a day for 14 days; or placebo orally, once a day for 14 days. The rationale for a treatment period of 14 days was based on the data from our prior study¹³ showing improvement of cachexia-related symptoms by day 10 of treatment with thalidomide. Because patients with advanced cancer have significant ACS and often are late referrals at the

TABLE 2. BASELINE ASSESSMENTS

Symptom variable	N	Mean(SD)	Median(Range)
Fatigue (ESAS)	31	6.19 (2.1)	7 (2–10)
Pain (ESAS)	31	3.1 (2.57)	7 (0–10)
Depression (ESAS)	31	3.16 (2.57)	3 (0–8)
Appetite (ESAS)	31	6.35 (2.2)	6 (3–10)
FACIT-F subscale	31	20 (7)	20 (5–36)
FAACT	30	21.8 (7.7)	22 (7–36)
HADS: Anxiety	27	7.33 (4.08)	7 (4–10)
HADS: Depression	30	8.23 (4.43)	8 (4–12)
PSQI	28	10.42 (4.73)	10 (1–18)
Body weight	30	69 (16.51)	69.3 (56.8–82.6)
BIA: Bodymass index	30	22.6 (3.9)	21.7 (16.9–33.50)
BIA: Impedence	28	513.1 (119.6)	508 (433–606)
BIA: Body fat percent	27	21.7 (9.89)	16.6 (14.7–33.6)
BIA: fat mass	28	16.1 (9.5)	12.5 (9.2–21.9)
BIA: fat free mass	28	53.8 (11.4)	56 (42.2–61.1)
MedGem Resting Metabolic Rate	25	1502.3 (509.2)	1500 (1260–1910)

BIA, bioelectrical impedance analysis; ESAS, Edmonton Symptom Assessment Scale; FAACT, Functional Assessment of Anorexia/Cachexia Therapy; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Questionnaire Inventory.

time of presentation to the palliative care team, it is vitally important to obtain prompt control of ACS.^{18,19}

Outcome measures

Patient demographics and performance status were recorded during pretreatment assignment.

The following assessments were performed at baseline, day 15, and day 29.

Edmonton Symptom Assessment Scale

The Edmonton Symptom Assessment Scale (ESAS) was used to assess 10 symptoms commonly experienced by cancer patients during the previous 24 hours: pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, level of feeling of well-being, and other symptoms.²⁰ The ESAS is both valid and reliable in the assessment of the intensity of symptoms in cancer patients.²¹

Functional Assessment of Cancer Therapy

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale consists of 27 general quality-of-life questions divided into four domains (physical, social, emotional, and functional). The 13-item fatigue subscore is a patient-rated assessment of intensity of fatigue and its related symptoms on a scale of 0 to 4. This scale has been shown to have strong internal consistency ($\alpha = 0.93\text{--}0.95$).²²

The FAACT is a 12-item symptom-specific subscale of the Functional Assessment of Cancer Therapy-General (FACT-G) scale designed to measure patients' additional concerns about their anorexia-cachexia during the previous 7 days. The FAACT has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.88 for its 12 components.²²

Hospital Anxiety and Depression Scale

Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS). This 14-item questionnaire has been validated in a number of clinical situations and has been widely used in medically ill patients.²³

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Questionnaire Inventory (PSQI) is an effective instrument for measuring the quality and patterns of sleep. The PSQI has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.83 for its seven components. Numerous studies using the PSQI have supported its high validity and reliability.²⁴

Bioelectrical impedance

The Tanita bioelectrical impedance analysis (BIA) body composition scale (Tanita Corporation of America, Inc., Arlington Heights, IL) was used to measure body composition indices. The patient's resting metabolic rate (RMR) was measured using a calorimetry device (MedGem, Health Tech, Golden, Co). It has been reported that RMR is elevated in cancer patients with cachexia as compared with those without.¹²

Cytokine levels

Prior studies have shown that ACS is associated with dysregulation of inflammatory cytokines.^{10,11} In this study,

TABLE 3A. CHANGE IN SYMPTOMS OVER TIME

Variable	Thalidomide group				Placebo group					
	Baseline (n = 15)	Day 15 (n = 9)		Day 29 (n = 6)		Baseline (n = 16)	Day 15 (n = 12)		Day 29 (n = 12)	
	Median (range)	Median (range)	P value ^a	Median (range)	P value ^b	Median (range)	Median (range)	P value ^a	Median (range)	P value ^b
ESAS: Pain	3 (0–8)	3 (0–10)	0.24	4 (0–8)	0.57	3 (2–5)	6.5 (0–5)	0.39	2.5 (0.25–3)	0.52
ESAS: Fatigue	7 (2–8)	5.5 (1–9)	0.52	5 (2–6)	0.85	6.5 (4.25–8)	5 (2.5–5.5)	0.04	5 (3.25–8)	0.28
ESAS: Appetite	6 (3–10)	4.5 (1–8)	0.10	7 (0–10)	0.27	6.5 (0–5)	3 (2–7)	0.01	5.5 (2.25–8)	0.08
ESAS:	6 (3–10)	1.5 (0–7)	0.14	2 (0–5)	0.41	2.5 (0–4.7)	2 (0–3)	0.13	2 (0–3.75)	0.67
Depression										
FAACT	22.5 (9–36)	32 (13–38)	0.14	25 (19–38)	0.59	22.5 (19–32)	28 (21–32)	0.08	27 (22–39)	0.61
FACIT-F	21 (7–35)	24.5 (4–39)	0.07	16 (9–34)	0.1	20 (15.5–25)	24 (17–31)	0.15	24 (18–32)	0.02
HADS-A	9 (2–16)	9 (1–9)	0.12	6 (5–10)	0.33	7 (4–9)	4 (2–10)	0.13	6.5 (4.2–10)	0.27
HADS-D	10 (4–17)	8 (3–13)	0.67	8 (4–15)	0.25	8 (3–10)	8.5 (3–12)	0.32	6.59 (4.2–10)	0.72
ISI	9.5 (7.5–14.7)	10.5 (5.25–12.7)	0.49	8 (3–10)	0.059	11 (5.2–15)	8.5 (3.25–13.5)	0.25	8 (4–12)	0.34

^ap value: Wilcoxon signed-rank test for day 15-baseline.

^bP value: Wilcoxon signed-rank test for day 15-baseline.
^cP value: Wilcoxon signed-rank test for day 29-day 15.

^a P value: Wilcoxon signed-rank test for day 29–day 15.
BIA, bioelectrical impedance analysis; ESAS, Edmonton Symptom Assessment Scale; FAACIT, Functional Assessment of Anorexia/Cachexia Therapy; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index.
P ≤ 0.05 = statistically significant (bold).

TABLE 3B. CHANGE IN BODY COMPOSITION AND RESTING METABOLIC RATE OVER TIME

Variable	Thalidomide group				Placebo group			
	Day 15 (n=9)		Day 29 (n=7)		Day 15 (n=9)		Day 29 (n=7)	
	Median (range)	P value ^a	Median (range)	P value ^b	Median (range)	P value ^a	Median (range)	P value ^b
BIA: weight in kg	67.4 (54.2–82.1)	0.16	62.8 (49.7–82.1)	0.49	69.8 (57.5–82.6)	0.63	79.4 (62–95.4)	0.55
BIA: Body mass index	21.1 (20.2–25.4)	0.09	21.2 (20.75–23.8)	0.75	22.3 (19.4–26.9)	0.88	22.1 (19.1–26.9)	0.34
BIA: Impedance	569 (378–610)	0.01	445 (316–522)	0.71	494 (437–596)	0.37	493 (359–587)	0.31
BIA: Body fat percent	17.3 (15.5–34.1)	0.01	14 (4.25–34.1)	0.71	15.8 (14.6–28.8)	0.32	23 (14.8–31)	0.29
BIA: Fat mass	13 (7.4–21.8)	0.03	11.5 (5.9–18.6)	0.71	10.4 (9.5–23.5)	0.27	20 (9.2–22.4)	0.08
BIA: Fat free mass	56.2 (6–18)	0.024	51 (40.2–69.6)	1.0	59.6 (45.9–62.1)	0.90	61.2 (50.8–74.4)	0.34
MedGem Resting Metabolic Rate	1380 (1279)	0.68	1715 (1215–1885)	0.58	17.50 (1095–1940)	0.62	1850 (1530–2000)	0.75

^aP value: Wilcoxon signed-rank test for day 15–baseline.^bP value: Wilcoxon signed-rank test for Day 29–Day 15.

BIA, bioelectrical impedance analysis.

P≤0.05 = statistically significant (bold).

TABLE 3C. CHANGE IN SERUM CYTOKINES AND RECEPTORS OVER TIME

Variable in pg/mL	Thalidomide group				Placebo group			
	Baseline (n=5)		Day 15 (n=5)		Baseline (n=10)		Day 15 (n=10)	
	Median (quartile)	P value ^a	Median (quartile)	P value ^a	Median (quartile)	P value ^a	Median (quartile)	P value ^a
IL-6	54.1 (16.8–280.3)	0.88	85 (18–140)	0.88	76.4 (19.1–133)	–6.51 (–37.9–26.4)	–6.51 (–37.9–26.4)	0.005
IL-1b	0.52 (0.32–0.74)	0.67	0.67 (0.29–2.77)	0.67	0.83 (0.22–1.4)	0.57 (0.43–0.68)	0.57 (0.43–0.68)	0.91
IL-1RA	677 (501–784)	0.06	290.7 (–901–515)	0.06	579 (266–755)	102.3 (–639.6–356.3)	102.3 (–639.6–356.3)	0.005
TNF-α	18.2 (13.8–123.1)	0.67	6.4 (–24.8–108.8)	0.043	21.2 (17.8–37.1)	6.24 (–12.8–14.6)	6.24 (–12.8–14.6)	0.008
IL-17	3.2 (1.75–39.7)	0.67	9.2 (3.1–17)	0.67	12.07 (4.3–122.6)	11 (3.4–316.3)	11 (3.4–316.3)	0.57
IL-8	36.1 (29.7–68.1)	0.67	2.12 (–7.5–11.2)	0.043	139.9 (54.1–289.1)	–3.7 (–20.9–50.3)	–3.7 (–20.9–50.3)	0.005
IL-6R	6264 (4321–30159)	0.34	5446 (3530–16596)	0.34	13567.4 (7186–17165.4)	10059.7 (5117–19944)	10059.7 (5117–19944)	0.28
TNFR1	2007.2 (418.6–2593.2)	0.043	–77.2 (–161.7–604.6)	0.043	6788 (793.1–3400.9)	99.4 (–356.4–539.8)	99.4 (–356.4–539.8)	0.005
TNFR2	8788 (3286–21126)	0.043	75.4 (–693–4319)	0.043	6788.2 (5440–14446)	–107.8 (–1726–1766)	–107.8 (–1726–1766)	0.005
IL-10	2.58 (1.66–7.77)	0.6555	2.58 (1.6–7.7)	0.6555	2.83 (1.31–4.93)	2.6 (1.4–6.8)	2.6 (1.4–6.8)	0.73

^aP value: Wilcoxon signed-rank test.

IL, interleukin; TNF, tumor necrosis factor.

P≤0.05 = statistically significant (bold).

TABLE 4. ADVERSE EVENTS EXPERIENCED PER PATIENTS IN THALIDOMIDE AND PLACEBO GROUPS

Toxicity	Thalidomide; n = 16		Placebo; n = 15		<i>P</i> ^a
	Grade ^b 1/2	Grade 3 or more	Grade1/2	Grade 3 or more	
Anemia	4	2	5	2	NS
Constipation	4	1	7	1	NS
Diahrrhea	1	0	1	0	NS
Dizziness	3	1	5	0	NS
Drowsiness	4	0	5	1	NS
Infection	0	2	2	1	NS
Insomnia	4	0	5	1	NS
Numbness	1	0	6	0	NS
Rash	1	0	3	0	NS
Thromboembolism	0	0	0	1	NS

^a χ^2 test.^bGrading was in accordance with National Cancer Institute Common Toxicity Criteria version 3.0.

we measured the levels of IL-1 β and its receptor IL-1RA, IL-6 its receptor IL-6R, and TNF- α and its receptors TNFR1, TNFR2, IL-10, and IL-8 to determine the effects of thalidomide and placebo on these inflammatory cytokines. The cytokines were measured in the serum by multiplex bead immunassay using a Luminex™ kit (Millipore Corp., Billerica, MA). Serum IL-10, IL-1 β , IL-1RA, IL-6R, sTNF-RI, and sTNF-R2 were also analyzed by Quantikine using an enzyme-linked immunosorbent assay device from ELISA (R&D) Systems Inc., Minneapolis, MN) as the signals obtained proved undetectable using the Multiplex bead immunoassay.

Adverse events were assessed in accordance with National Cancer Institute Common Terminology Criteria (NCI CTC) version 3.0 criteria.

Statistical considerations

We summarized the demographics and subjective and objective outcomes. We analyzed the change in the symptom measures (ESAS fatigue, pain, depression, and appetite items; FACIT-F; FAAct; HADS; and PSQI) using the Wilcoxon signed-rank test (nonnormally distribution). We also compared the differences in using χ^2 (Fisher's exact test for lesser variables) and the Mann-Whitney U test in the thalidomide and placebo groups.

Results

Patient accrual information

Of the 31 patients in the study, 15 were assigned to the thalidomide and 16 to the placebo group. Of the total 31 patients, 10 patients dropped out (6 patients from the thalidomide and 4 from the placebo arm) prior to day 15 (primary endpoint); of these 10 dropouts, 4 were hospitalized because of disease progression; 3 were nonadherent; one was unavailable for contact; and 2 never received the study drug after randomization.

The patients' characteristics are summarized in Table 1. There were no significant differences between the two study arms based on any demographic characteristics such as age, sex, cancer types, or appetite as measured by ESAS and FAAct ($p \geq 0.1$; data not shown).

Table 2 shows the intensity of symptoms at baseline in all patients.

Table 3a–c shows the ACS variables and cytokine levels in the thalidomide and placebo groups at baseline, day 15, and day 29. The improvement in these symptoms and cytokine levels was not significantly different in the thalidomide or the placebo group.

Table 4 summarizes the adverse events of the thalidomide and placebo group.

Discussion

The findings in this study suggest the limitations associated in conducting a randomized controlled trial of thalidomide for the treatment of ACS in patients with advanced cancer. Various reasons were identified for the lack of accrual. These include limited number of eligible patients due to the stringent exclusion and inclusion process and monitoring involved; in addition, there were concerns about possible drug interactions with the prescribed cancer treatment and about taking a placebo. Another limitation was the dropouts. Reasons for dropouts included nonstudy-related hospitalization, nonadherence, discharge to hospice, and family not interested in continuing in the study. Based on the experience from the study, perhaps future anorexia-cachexia treatment trials in patients with advanced cancer should use less stringent entry criteria and less exhaustive outcome measures.

Surprisingly, we also found significant reduction of cytokines TNF- α , and its receptors (TNFR1, TNFR2), IL-1RA (placebo only), IL-6, and IL-8 in the patients who received placebo and who received thalidomide. However, the decrease in the cytokines could be related to the discontinuation of previous chemotherapy.

Compared with prior studies,^{4,7,13,15} this is the first to investigate the effect of thalidomide and placebo using validated ACS measures and cytokines. However compared with prior studies, our sample size was smaller, we had a high rate of the attrition, and noncompliance rates were higher.^{7,14}

We found that there was no significant difference in the toxicity related to the treatment with thalidomide as compared with placebo (Table 4). These results were similar to those of prior studies by our team and of studies by others on the safety of low-dose thalidomide.^{7,8,13–15} Further studies are needed on the use of thalidomide for ACS based on preliminary safety and efficacy data from prior studies. It is possible that the drug may be of particular utility in the developing world due to its low cost and easy access.

Conclusions

Based on the poor accrual rate and attrition observed in this study, it is important that future research on thalidomide as a treatment for cancer-related ACS in patients with advanced cancer use less stringent entry criteria and less exhaustive outcome measures. Further studies using thalidomide for the treatment of anorexia-cachexia are needed.

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Author Disclosure Statement

No competing financial interests exist.

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