JOURNAL OF CLINICAL ONCOLOGY

Comparison of Orally Administered Cannabis Extract and Delta-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial From the Cannabis-In-Cachexia-Study-Group

Florian Strasser, Diana Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Martin Schnelle, Marcus Reif, and Thomas Cerny

From the Division of Oncology/
Hematology, Department of Internal
Medicine, Cantonal Hospital, St Gallen,
Switzerland; Departments of Medical
Oncology and Anesthesiology/Pain
Management, University Hospital
Charité, Central Campus; Institute for
Clinical Research, Berlin; Department of
Anesthesiology and Intensive Care,
Friedrich-Schiller-University, Jena; and
Medizinische Poliklinik, University
Hospital, Bonn, Germany.

Address reprint requests to Florian
Strasser, MD, ABHPM, Oncology and
Palliative Medicine, Section of Oncology/
Hematology, Department Internal Medi-
cine, Cantonal Hospital,
Rorschacherstrasse, 9007 St Gallen,
Switzerland; e-mail: florian.strasser@
kssg.ch.

A B S T R A C T

Purpose
To compare the effects of cannabis extract (CE), delta-9-tetrahydrocannabinol (THC), and placebo (PL) on appetite and quality of life (QOL) in patients with cancer-related anorexia-cachexia syndrome (CACS).

Patients and Methods
Adult patients with advanced cancer, CACS, weight loss ($\geq$ 5% over 6 months), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2 were randomly assigned (2:2:1) to receive CE (standardized for 2.5 mg THC and 1 mg cannabidiol) or THC (2.5 mg) or PL orally, twice daily for 6 weeks. Appetite, mood, and nausea were monitored daily with a visual analog scale (VAS); QOL was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (composite score: questions 29 and 30). Cannabinoid-related toxicity was assessed every 2 weeks.

Results
Of 289 patients screened, 243 were randomly assigned and 164 (CE, 66 of 95 patients; THC, 65 of 100 patients; and PL, 33 of 48 patients) completed treatment. At baseline, groups were comparable for age (mean, 61 years), sex (54% men), weight loss (32% $\geq$ 10%), PS (13% ECOG = 2), antineoplastic treatment (50%), appetite (mean VAS score, 31/100 mm), and QOL (mean score, 30/100). Intent-to-treat analysis showed no significant differences between the three arms for appetite, QOL, or cannabinoid-related toxicity. Increased appetite was reported by 73%, 58%, and 69% of patients receiving CE, THC, or PL, respectively. An independent data review board recommended termination of recruitment because of insufficient differences between study arms.

Conclusion
CE at the oral dose administered was well tolerated by these patients with CACS. No differences in patients' appetite or QOL were found either between CE, THC, and PL or between CE and THC at the dosages investigated.

J Clin Oncol 24:3394-3400. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Anorexia and weight loss contribute to cancer-related fatigue, functional loss, impaired survival, and intolerance of treatment.[1,2] Efforts to palliate these conditions include studies of the endocannabinoid system, which modulates appetite[3] through cannabinoid receptor–related processes.[4] Hyperphagic effects of cannabinoids[5] and hypophagic actions of selective cannabinoid receptor antagonists[6] have been reported.

Cannabis sativa contains over 60 cannabinoids, including delta-9-tetrahydrocannabinol (dronabinol, THC) and cannabidiol (CBD).[7] THC, its major psychoactive component, is an antiemetic medication.[8] CBD reportedly reduces the psychotropic effects of THC and has anti-inflammatory effects.[9]

Cannabinoids reputedly stimulate appetite, both historically[10] and in recent studies of human volunteers[11-13] and AIDS patients.[14] Studies of patients with multiple sclerosis[15-17] or pain[18] have

evaluated oral mixtures of THC and CBD or whole-plant cannabis extract (CE), replacing smoked marijuana. Data from four dose-finding and phase II studies of 161 patients with cancer-related anorexia-cachexia syndrome (CACS) suggest cannabinoids' potential at fixed doses of 2.5 mg of THC twice to three times daily;[19-21] however, megestrol acetate palliated anorexia better than THC.[22] We investigated the effects of CE and THC on appetite and quality of life (QOL) in patients with CACS.

PATIENTS AND METHODS

This multicenter, phase III, randomized, double-blind, placebo (PL)-controlled, three-arm, parallel study, which was sponsored by the Institute for Clinical Research, Berlin, adhered to the Good Clinical Practice Program,[23] European Union Directive 91/507/EEC,[24] and the Declaration of Helsinki.[25] Participating centers obtained approval from their local institutional ethical review boards and health authorities.

Participants

Physicians recruited adult patients with advanced incurable cancer who were candidates for appetite stimulation, having had, within the past 6 months, involuntary weight loss of ≥ 5% not explained by other diseases or recent surgery. Eligible patients gave written informed consent to participate; could feed themselves; received no enteral or parenteral nutrition; had taken no anabolic agents, gestagens, cannabinoids, or corticosteroids (except for < 20 mg prednisolone for < 5 consecutive days) within the past month; and had no significant cause of secondary anorexia[2] or psychiatric disorder (substance abuse or schizophrenia). Patients had an estimated life expectancy of 3 months; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2; creatinine, bilirubin, and transaminase values no higher than 3× the maximum normal value; and unchanged antineoplastic therapy for 4 weeks and unchanged supportive treatment (analgesics, sedatives, tranquilizers, and anticholinergics) for 1 week before baseline assessments.

Intervention

After 7 to 14 days of baseline assessment, eligible patients were randomly assigned to treatment with PL, CE, or THC for 6 weeks. Patients received a 2-week supply of capsules to take orally twice daily (1 hour before lunch and before dinner or at bedtime, preferably with milk).

All *C sativa* plants were harvested at once in Switzerland and processed into a fluid extract (Verein-für-Krebsforschung, Arlesheim, Switzerland) to prepare gelatin capsules containing CE (2.5 mg THC and 1 mg CBD) or only THC (2.5 mg). PL capsules containing standardization medium (Hüls-AG, Marl, Germany) were indistinguishable from the active capsules. Encapsulation was uniformly processed by Scherer-GmbH (Eberbach, Germany). The Unfallkrankenhaus (Berlin, Germany) packed the drug.

Objectives

We tested the hypotheses that appetite and QOL improve significantly in patients treated with THC or whole-plant CE compared with PL[26] and that CE and THC have equivalent effects on appetite and QOL.

Outcome Measures

Assessments were performed every 2 weeks during clinic visits at screening, at random assignment when treatment began (week 0), and at weeks 2, 4, and 6; patients kept a diary. At each visit, patients underwent an examination evaluating vital signs and ECOG PS and a test for urinary cannabinoids.

A primary end point was appetite change from baseline to week 6, assessed with a visual analog scale (VAS; 0 mm = worst; 100 mm = best). Appetite values were calculated as the mean of daily appetite VAS scores for the 7 days of week 2 in each biweekly period. The second primary end point was the change in QOL from baseline to week 6 (composite score [mean] of questions 29 [Global Health Status] and 30 [QOL] on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 [EORTC QLQ-C30], transformed into a single functional scale [range, 0 to 100]).[27]

The EORTC QLQ-C30[27] was completed biweekly. Three other variables were monitored daily with a VAS: (1) patients' estimation of food intake during the previous 24 hours; and patients' current (2) feeling of nausea and (3) mood.

Two ad hoc EORTC QLQ-C30 modules, Anorexia-Cachexia and Cannabinoid Toxicity (CannTox), were completed biweekly. The first was translated from the Functional Assessment of Anorexia/Cachexia Therapy.[28] Its internal consistency (Cronbach's α = .76) and test-retest reliability (Pearson correlation between screening and randomization, r = 0.68) were good, as was the correlation (Spearman partial rank) of the total score with the EORTC QLQ-C30 question about appetite loss (r = −0.59; P < .0001) and with VAS scores for appetite (0.36 mm; P < .0001). The CannTox module was based on the Drug Reaction Scale of adjectives describing mood, physical feelings, and perceptions of mental or cognitive functions of healthy volunteers under the influence of cannabis.[29] Patients complied with study protocol if they took at least 90% of the prescribed medication over the study period, as based on the returned empty capsule blisters.

Adverse events (AEs) were classified according to Common Toxicity Criteria.[30] CBCs and biochemical and urine profile analyses were performed at each visit. In cases of study drug–related AEs, the dose was reduced to one capsule daily or was interrupted until the AEs resolved, at which point patients again took two capsules or resumed treatment with one capsule daily at bedtime. Serious AEs were evaluated by the Safety Review Committee (F.S., M.S., and T.C.).

Sample Size

Sample size was calculated with reference to a study of THC used to treat AIDS-related anorexia,[14] which showed a mean increase in appetite of 15 mm from baseline (standard deviation [SD], 15 mm) on a VAS in the verum group and 7.4 mm in the PL group. Half of SD may be considered clinically significant.[31]

To compare CE and THC with PL, a two-tailed test of differences from baseline to week 6 in appetite score was planned (significance level, 5%; power, 90%; expected between-group difference, 7 mm). For the noninferiority test of CE against THC, a one-tailed test was planned (significance level, 2.5%; power, 90%; maximum lower deviation of CE, 6 mm). For both tests, an SD of 15 mm in all three groups was assumed. The required sample was 133 patients per verum group and 68 patients in the PL group (treatment allocation in a 1:2:2 ratio). Assuming a dropout rate of 25%, the total sample was increased to 445 patients.

After a blinded interim analysis of 46 patients to assess data variability, the analysis plan was adjusted to a group sequential, adaptive trial with the permission of each center's ethical review board. An independent data review board recommended that the trial be closed after the first unblinded interim analysis of fully monitored data from 156 assessable patients because of insufficient differences in the primary end point between the PL and verum arms; recruitment stopped with 289 patients screened.

Treatment Assignment, Random Assignment, and Blinding

Patients were randomly assigned at the week 0 visit, after the baseline period. Random assignment lists, stratified by center, were prepared by a naive statistician using SAS software (SAS Institute, Cary, NC).[32] Centers received study drug sets in multiples of five, together with matching sealed envelopes containing individual treatment assignments. Investigators remained blinded until the study ended, with individual unblinding permitted only for safety reasons. The statistician and data manager who were managing random assignment, unblinding, and related decisions were naive to clinical evaluations and uninvolved in data management or analysis.

Statistical Analyses

All analyses were performed with SAS.[32] One interim analysis was performed for the independent data review board (156 patients) and one for presentation (216 patients).[33]

Descriptive statistics were used for demographic and baseline variables. For efficacy analyses, the groups of patients enrolled before the first interim analysis, in between the two analyses, and after the second interim analysis were treated as independent samples of the whole population[34,35]; the three resulting test statistics were properly combined, holding an overall one-sided

significance level of $P = .025$ partitioned into $P = .00025$, $P = .00691$, and $P = .02221$, respectively, regarding the three successive analyses.

The confirmatory test for superiority of any verum arm over PL was based on the intent-to-treat (ITT) population. For confirmation of noninferiority of CE to THC, the per-protocol (PP) population was used.

An a priori ordered cascade of statistical testing of six null hypotheses was applied[36] in each interim and final analysis as follows: H_0^{1-3} for appetite, CE versus PL, then THC versus PL, then CE versus THC; and H_0^{4-6} for QOL in the same sequence. The significance of each statistical test could be deduced confirmatively only if the actual and all higher order tests had yielded P values smaller than the actual critical significance level.

For the ITT population, missing values were substituted by the nearest-neighbor approach.[37] Sensitivity analysis additionally analyzed all efficacy parameters by the last observation carried forward method and by the worst-case approach.[38]

Verum and PL groups were compared using analysis of covariance, including treatment as a fixed factor and the VAS or QOL baseline values as continuous covariates. Center effects were ignored because of the many centers with only a few patients.[39] Additionally, one-sided 97.5% CIs for differences were given.

All successive tests were considered exploratory. For mood, nausea, daily food intake, and EORTC QLQ-C30 items, changes from baseline to weeks 2, 4, and 6 were analyzed analogous to the primary end points. Additional exploratory analyses were performed in subgroups based on preliminary evidence of distinguishable CACS with high versus low C-reactive protein (CRP), in different tumor types, by sex, and by degree of weight loss.[1,2]

For all safety parameters, descriptive statistics over time was performed. P values were calculated as flagging devices to mark conspicuous, potentially clinically relevant differences. Treatment groups were compared regarding hazard rates of AEs by Cochran-Mantel-Haenszel χ^2 tests and regarding continuous data by analysis of variance. The proportions of patients not completing the study were compared between treatment groups by the χ^2 test.

RESULTS

Patients

Patients were recruited from October 1999 to September 2002 in 30 centers in Germany, Switzerland, and the Netherlands. Average weight loss was 11.9%; 46% of patients lost less than 10% of weight. Patient characteristics (Table 1) and the percentage of dropouts and the reasons for dropout (Fig 1) were similar between treatment arms. Compliance with treatment was similar between arms (CE, 49%; THC, 44%; and PL, 60%; $P > .15$); 84 patients had major protocol violations (16, 22, and nine patients on CE, THC, and PL, respectively) and/or less than 90% intake of the study medication (14, 10, and four patients on CE, THC, and PL, respectively), were missing primary end point data (three, one, and three patients on CE, THC, and PL, respectively), had THC in their serum at baseline (zero, three, and zero patients on CE, THC, and PL, respectively), or had other protocol deviations (four, three, and one patient on CE, THC, and PL, respectively). The PP analysis set comprised 80 patients (33%; 32, 31, and 17 patients on CE, THC, and PL, respectively), who were mostly men and older and had better baseline values for mood, nausea, daily food intake, and EORTC QLQ-C30 scores.

Appetite and Overall QOL

Pooled over all samples of the adaptive design, patients taking CE and PL, after 6 weeks, showed a similar mean improvement in appetite (mean, 5.4 mm; SD, 24.7 mm; and mean, 5.8 mm; SD, 23.8 mm, respectively), whereas patients taking THC showed only a 0.6-mm improvement (SD, 18.5 mm; Fig 2). No verum arms improved significantly compared with PL (combined test statistics:

Table 1. Baseline Characteristics of Patients With Cancer-Related Anorexia-Cachexia Syndrome Receiving CE, THC, or Placebo (N = 243)

Characteristic	Placebo (n = 48)	CE (n = 95)	THC (n = 100)
Age, years			
Mean	62	61	60
SD	10	12	12
Sex, % men	52	56	54
Malignancy, %			
Lung, head, and neck	23	24	19
GI, urogenital	56	57	48
Hematologic-lymphogenic	8	4	8
Other	13	15	25
Chemotherapy,* %	52	47	52
Weight loss in the past 6 months,† %			
5% to < 10%	21	45	45
10% to < 15%	14	30	33
≥ 15%	13	20	22
ECOG performance status, %			
0	13	16	12
1	81	69	74
2	6	15	14
Appetite,‡ VAS, mm			
Mean	36	33	32
SD	19	21	21
Nausea,‡ VAS, mm			
Mean	25	29	26
SD	22	25	24
Quality of life,§ %			
Mean	37	36	36
SD	18	20	20

Abbreviations: CE, cannabis extract; THC, delta-9-tetrahydrocannabinol; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; VAS, visual analog scale.

*Chemotherapy: patients who received chemotherapy in the 4 weeks before baseline and who intended to continue chemotherapy during the study.

†Involuntary weight loss not explained mainly by perioperative weight loss.

‡Measured by VAS: 0 = worst and 100 = best.

§Quality of life: mean of the two categorical scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, questions 29 (Global Health Status) and 30 (Quality of Life), transformed to a 0% to 100% scale (0 = best, 100 = worst).

$P = .46$ for comparison with CE; $P = .95$ for comparison with THC). The correlations of VAS appetite scores with the EORTC QLQ-C30 categoric scale of Appetite Loss in the three treatment groups were $r = -0.55$ for the absolute scores and $r = -0.45$ for the changes from baseline (Spearman rank correlation, $P < .0001$ at each comparison). Increased appetite (best biweekly value over baseline) was reported by 75%, 60%, and 72% of patients receiving CE, THC, and PL, respectively ($P = .068$).

Mean overall QOL after 6 weeks showed nearly no change from baseline and was not different for PL compared with CE ($P = .80$) or THC ($P = .43$) from combined test statistics (mean score change ± SD: CE, 1.1 ± 19.2; THC, 5.1 ± 21.2; and PL, 3.0 ± 19.5; Fig 3). The test for noninferiority of CE compared with THC (PP population) showed no significant difference ($P = .90$, combined).

Other Symptoms, Functional Domains of QOL, and Body Weight

From patients with a baseline VAS nausea score of ≥ 30 mm one CE (40 of 95 patients), THC (36 of 96 patients), or PL (16 of 46
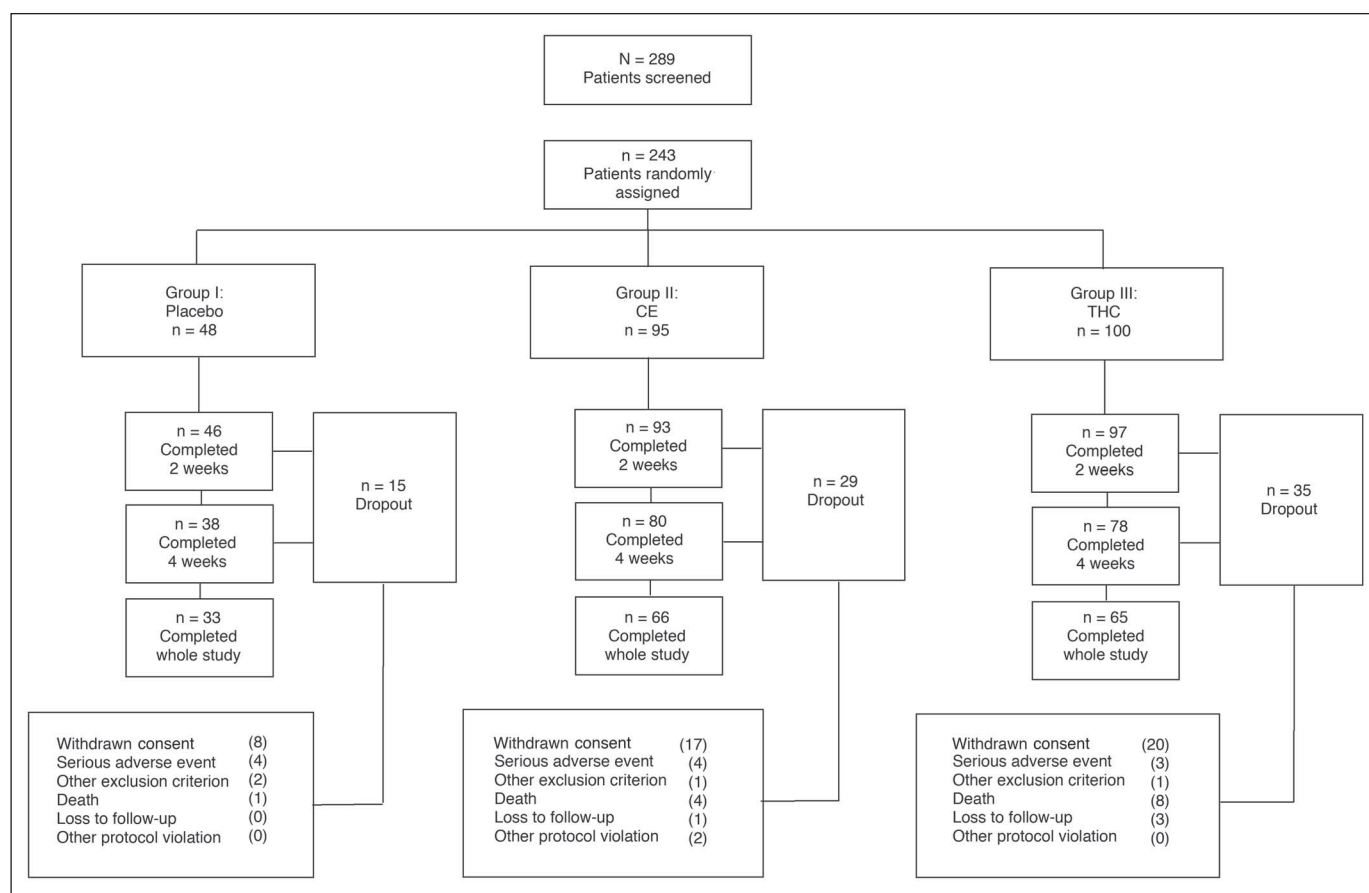
Fig 1. Patient flow. N, number; CE, cannabis extract; THC, delta-9-tetrahydrocannabinol.

patients), an improvement, which was defined as a VAS score less than 30 mm, was seen in 61%, 50%, and 40%, respectively (*P* = .367). The respective results for mood were 60%, 46%, and 64% (*P* = .461) in patients on CE (33 of 95 patients), THC (25 of 96 patients), and PL
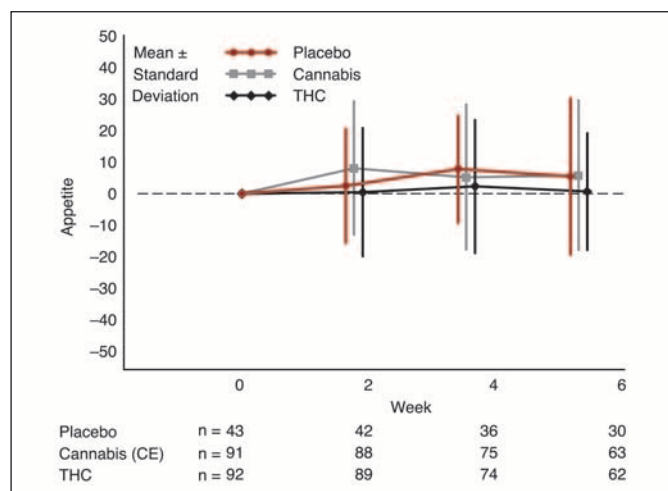

Fig 2. Changes in visual analog scale (VAS) scores from baseline for appetite in the intent-to-treat population. THC, delta-9-tetrahydrocannabinol. Appetite represents mean of daily appetite VAS scores for the 7 days of week 2 in each biweekly period of the 6-week study period.

(12 of 46 patients). A steady-state or slight deterioration was observed in all treatment arms for EORTC QLQ-C30 functional scales and for the following items: physical, role, emotional, cognitive, and social functioning; and dyspnea, diarrhea, and financial problems. All treatment arms showed a 5% improvement in the overall score (arithmetic mean) on the Anorexia-Cachexia EORTC QLQ-C30 module until week 2, followed by another 5% improvement until week 6 in the PL group, steady-state with THC, and worsening by 2.5% with CE. No differences between groups in body weight at baseline or week 6 (average, 61 kg) or in weight loss (average, 600 g in 6 weeks) were reported.

Subgroup Analyses

Among patients receiving CE or THC compared with PL, appetite scores higher than the average score over the whole ITT population were found in exploratory analyses of subgroups for women (6.8 mm for CE, 3.1 mm for THC, and −2.8 mm for PL) and for patients with tumors other than hematologic-lymphogenic; head, neck and lung; or GI-urogenital (1.8 mm for CE, 3.1 mm for THC, and −2.1 mm for PL). Patients with CRP values ≥ 10 mg/L at baseline (1.4 for CE; 2.5 for THC; and −5.5 for PL) had mean overall QOL scores higher than the ITT average. Patients with various degrees of weight loss showed no differences.

AEs

There were no differences between treatment arms for vital signs or ECOG PS. There were 526 AEs (CE, n = 238; THC, n = 197; and
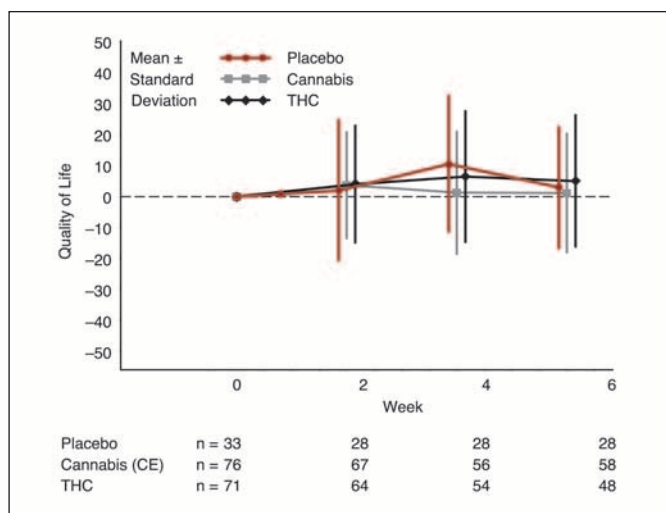
Fig 3. Changes in visual analog scale (VAS) scores from baseline for quality of life (QOL) in the intent-to-treat population. QOL values represent composite scores (mean) of questions 29 (Global Health Status) and 30 (QOL) on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 transformed into a single functional scale (range, 0 to 100). THC, delta-9-tetrahydrocannabinol.

PL, n = 91); their relationship to the study medication was none or unlikely for 415 AEs (CE, n = 201; THC, n = 144; and PL, n = 70), probable for 90 AEs (CE, n = 28; THC, n = 45; and PL, n = 17), and likely for 20 AEs (CE, n = 9; THC, n = 7; and PL, n = 4). Temporary or permanent dose reductions were necessary in 78 patients (CE, n = 34; THC, n = 30; and PL, n = 14).

AEs occurring more than 10 times were nausea (CE, n = 23; THC, n = 21; and PL, n = 11), fatigue (CE, n = 16; THC, n = 14; and PL, n = 4), pain (CE, n = 11; THC, n = 17; and PL, n = 5), anemia (CE, n = 9; THC, n = 14; and PL, n = 6), dizziness (CE, n = 9; THC, n = 11; and PL, n = 7), dyspnea (CE, n = 9; THC, n = 7; and PL, n = 2), diarrhea (CE, n = 6; THC, n = 7; and PL, n = 2), and obstipation (CE, n = 6; THC, n = 7; and PL, n = 2). Table 2 lists the AE hazard rates. Of all AEs, 241 were mild (CE, n = 104; THC, n = 101; and PL, n = 36), 227 were moderate (CE, n = 113; THC,

Table 2. Maximum Toxicities Reported by Patients With Cancer-Related Anorexia-Cachexia Syndrome Receiving CE, THC, or Placebo (N = 243)

Toxicity	Hazard Rate*			P (over all groups)†
	Placebo (n = 48)	CE (n = 95)	THC (n = 100)	
Nausea/vomiting	0.065	0.067	0.060	.93
Fatigue	0.024	0.046	0.040	.44
Pain	0.029	0.032	0.049	.42
Anemia	0.035	0.026	0.040	.61
Vertigo	0.041	0.026	0.032	.65
Dyspnea	0.012	0.026	0.020	.55
Diarrhea	0.012	0.017	0.020	.84
Obstipation	0.012	0.017	0.020	.84

NOTE. Absolute frequencies ≥ 10 over all groups.
Abbreviations: CE, cannabis extract; THC, delta-9-tetrahydrocannabinol.
*Frequency of adverse event per patient and clinic visit.
†Overall test between three treatment arms: P < .0003; odds ratio for CE versus PL = 1.93 (95% CI, 1.30 to 2.87).

n = 71; and PL, n = 43), and 57 were severe (CE, n = 21; THC, n = 24; and PL, n = 12); one AE was undetermined. Severe AEs were mainly dizziness, nausea/vomiting, and dyspnea.

In total, 82 serious AEs[30] emerged (CE, n = 32; THC, n = 33; and PL, n = 17); diagnoses recorded at least five times were dyspnea (CE, n = 5; THC, n = 8; and PL, n = 3), tumor progression (CE, n = 5; THC, n = 8; and PL, n = 2), vomiting (CE, n = 8; THC, n = 8; and PL, n = 1), worsening of general well-being (CE, n = 2; THC, n = 9; and PL, n = 1), death (CE, n = 4; THC, n = 6; and PL, n = 1), pain (CE, n = 2; THC, n = 4; and PL, n = 4), fever (CE, n = 3; THC, n = 2; and PL, n = 2), diarrhea (CE, n = 3; THC, n = 2; and PL, n = 0), and exsiccation (CE, n = 1; THC, n = 3; and PL, n = 1). Thirteen serious AEs were life threatening (CE, n = 6; THC, n = 6; and PL, n = 1), 68 required hospitalization (CE, n = 25; THC, n = 27; and PL, n = 16), and one was unexpected by the physician (CE, n = 1; THC, n = 0; and PL, n = 0). No differences were found for the CannTox scales for dizziness, feeling good, feeling high, hallucinations, heart beating, panic attacks, feeling active, or walking insecurely.

DISCUSSION

This is the first phase III trial in patients with CACS comparing the effects of cannabinoids with PL and standardized CE, an integral total product of medical cannabis. We found no differences between the three groups over 6 weeks of treatment for the primary end points of appetite and QOL, for cannabinoid-related toxicity, or for secondary end points such as mood or nausea. Like the recent North Central Cancer Treatment Group (NCCTG) phase III trial using the same dose of THC, in which 49% of patients receiving THC had better appetite at least once during the study,[22] our study showed biweekly appetite scores higher than baseline values at some point during the trial in more than 50% of patients in all three groups. Like previous trials for symptom control, our study showed significant PL effects.[26] No differences in toxicity ascribed to cannabinoids were found between treatment arms in either this or the NCCTG phase III trial.[22]

Our rationale for choosing the daily dose of THC 5 mg was based on the following: (1) the study results available in the late 1990s, which suggested that THC 2.5 mg twice daily is the optimal dose[19,20]; (2) the lack of evidence of a clear dose-effect relationship requiring a trial design of individual dose titration; and (3) regulatory realities in this first trial with CE as a schedule 1 substance approved in the European Union, namely, the great caution regarding psychotropic adverse effects of cannabinoids. In a PL-controlled phase II trial with THC 0.1 mg/kg/d for 7 days, 20 of 54 patients dropped out; six patients dropped out as result of drowsiness, thinking problems, and panic reactions.[19] In a comparison of four doses of THC (2.5 or 5 mg, once or twice daily) over 6 weeks, 10 of 42 patients (eight taking 5 mg) dropped out because of drowsiness, memory problems, or mood changes. Only patients receiving THC 2.5 mg twice daily (47%) reported increased appetite.[20] In a study of 19 patients taking THC 2.5 mg three times daily over 4 weeks, four patients dropped out, and 13 of 18 patients had increased appetite.[21]

The secondary end point, weight, requires cautious interpretation because, in contrast to other trials lasting 8 to 12 weeks or longer, this trial was only 6 weeks long; however, in some of those trials, weight gain was observed after 4 weeks.[47,48] The degree of weight loss in our patients was lower (11.9%) than in other trials (17%[47] and 13%[48]). Of

our patients, 46% had less than 10% weight loss, whereas in the NCCTG trials,[22,49] 40% lost less than 5 pounds (approximately 7%).

Our trial reflects the challenges of a symptom-control trial in patients with advanced cancer, including a wide SD of symptom scores; substantial PL effect; the clinical reality of interfering symptoms and complications, adverse effects, and interactions of other medications; and a dropout rate of approximately 20% within 6 weeks. Nonetheless, we think the effects detected represent the actual effects with CACS in this real-life setting.[40]

Pathophysiologic features of CACS may partially explain the limited therapeutic effect of CE.[41] Cannabinoids appear to influence cytokines[9,42] but to insufficiently target the proinflammatory cytokines mediating CACS (tumor necrosis factor alpha, interleukin-1, and interleukin-6).[43] THC reduces GI motility,[44] which often is already impaired in patients with CACS.[45] Efforts are being made to characterize distinct CACS subtypes based on CRP levels,[46] pro-

nounced early satiety, or chronic nausea,[45] but our exploratory analysis detected no trend toward a better response to CE among putative subgroups of CACS or patients with different tumor types or degrees of weight loss.

Limitations of this study include the lack of intrapatient dose escalation of CE to test whether CBD may protect from dose-limiting THC adverse effects. The 6-week duration was short but sufficient to detect the potential of CE to change appetite loss and other symptoms. Although all investigators were trained in the procedures to be used in obtaining outcome measures, variations among centers may have affected uniformity of the data. Our stratification and block randomized design should control adequately for this potential limitation.

In conclusion, CE was well tolerated by patients but was associated with a higher hazard rate for AEs than PL. CE and THC, each with THC 2.5 mg, taken twice daily improved appetite and QOL no more than PL in patients with advanced cancer.

REFERENCES

1. MacDonald N: Is there evidence for earlier intervention in cancer-associated weight loss? J Support Oncol 1:279-286, 2003

2. Strasser F, Bruera ED: Update on anorexia/cachexia. Hematol Oncol Clin North Am 16:589-617, 2002

3. Cota D, Marsicano G, Lutz B, et al: Endogenous cannabinoid system as a modulator of food intake. Int J Obes Relat Metab Disord 27:289-301, 2003

4. Di Marzo V, Goparaju SK, Wang L, et al: Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 410:822-825, 2001

5. Kirkham TC, Williams CM, Fezza F, et al: Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: Stimulation of eating by 2-arachidonoyl glycerol. Br J Pharmacol 136:550-557, 2002

6. Fride E, Ginzburg Y, Breuer A, et al: Critical role of the endogenous cannabinoid system in mouse pup suckling and growth. Eur J Pharmacol 419:207-214, 2001

7. Grotenhermen F: Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 42:327-360, 2003

8. Tramer MR, Carroll D, Campbell FA, et al: Cannabinoids for control of chemotherapy induced nausea and vomiting: Quantitative systematic review. BMJ 323:16-21, 2001

9. Sacerdote P, Martucci C, Vaccani A, et al: The nonpsychoactive component of marijuana cannabidiol modulates chemotaxis and IL-10 and IL-12 production of murine macrophages both in vivo and in vitro. J Neuroimmunol 159:97-105, 2005

10. Nahas GG: Hashish in Islam 9th to 18th century. Bull N Y Acad Med 58:814-831, 1982

11. Abel EL: Effects of marijuana on the solution of anagrams, memory and appetite. Nature 231:260-261, 1971

12. Foltin RW, Fishman MW, Brady JV: Behavioral analysis of marijuana effects on food intake in humans. Pharmacol Biochem Behav 25:577-582, 1986

13. Foltin RW, Fischman MW, Byrne MF: Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite 11:1-14, 1988

14. Beal JE, Olson R, Laubenstein L, et al: Dronabinol as a treatment for anorexia associated with

weight loss in patients with AIDS. J Pain Symptom Manage 10:89-97, 1995

15. Zajicek J, Fox P, Sanders H, et al: Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): Multicentre randomised placebo-controlled trial. Lancet 362:1517-1526, 2003

16. Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al: Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled, crossover study. Mult Scler 10:417-424, 2004

17. Killestein J, Hoogervorst ELJ, Reif M, et al: Safety, tolerability, and efficacy of orally administered cannabinoids in MS. Neurology 58:1404-1407, 2002

18. Berman JS, Symonds C, Birch R: Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: Results of a randomised controlled trial. Pain 112:299-306, 2004

19. Regelson W, Butler JR, Schulz J, et al: Tetrahydrocannbinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients, in Braude MC, Szara S (eds): The Pharmacology of Marijuana: A Monograph of the National Institute of Drug Abuse. New York, NY, Raven, 1976, pp 763-776

20. Plasse TF, Gorter RW, Krasnow SH, et al: Recent clinical experience with dronabinol. Pharmacol Biochem Behav 40:695-700, 1991

21. Nelson K, Walsh D, Deeter P, et al: A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. J Palliat Care 10:14-18, 1994

22. Jatoi A, Windschitl HE, Loprinzi CL, et al: Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group Study. J Clin Oncol 20:567-573, 2002

23. United States Food and Drug Administration, Department of Health and Human Services: FDA Good Clinical Practice Program. http://www.fda.gov/oc/gcp/regulations.html

24. European Union Directive 91/507/EEC: Commission Directive 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. http://europa.eu.int/smartapi/cgi/

sga_doc?smartapi!celexapi!prod!CELEXnumdoc&numdoc=31991L0507&model=guichett&lg=en

25. The World Medical Association: The World Medical Association: Policy: World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. http://www.wma.net/e/policy/b3.htm

26. Chvetzoff G, Tannock IF: Placebo effects in oncology. J Natl Cancer Inst 95:19-29, 2003

27. Fayers PM, Aaronson NK, Bjordal K, et al: The EORTC QLQ-C30 Scoring Manual (ed 2). Brussels, Belgium, European Organization for Research and Treatment of Cancer, 1999

28. Ribaudo JM, Cella D, Hahn EA, et al: Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Qual Life Res 9:1137-1146, 2000

29. Musty RE: Individual differences as predictors of marijuana phenomenology, in Marijuana: An International Research Report. Proceedings of the Melbourne Symposium on Cannabis, 2-4 September 1987, monograph series no. 7. Canberra, Australia, Australian Government Publishing Service, 1988

30. Cancer Therapy Evaluation Program: Common Toxicity Criteria, Version 2.0. http://ctep.info.nih.gov/reporting/CTC-3test.html

31. Sloan JA, Cella D, Frost M, et al: Assessing clinical significance in measuring oncology patient quality of life: Introduction to the symposium, content overview, and definition of terms. Mayo Clin Proc 77:367-370, 2002

32. SAS Institute Inc: SAS Screen Control Language: Syntax, Version 6 (ed 1). Cary, NC, SAS Institute Inc, 1992, pp 124

33. Cerny T, Lueftner D, Possinger K, et al: Oral cannabis extract (CE) versus delta-9-tetrahydrocannabinol (THC) for patients with cancer-related anorexia (CRA): A randomized, double-blind, placebo-controlled multicenter study. Proc Am Soc Clin Oncol 22:730, 2003 (abstr 2934)

34. Bauer P, Köhne K: Evaluation of experiments with adaptive interim analyses. Biometrics 50:1029-1041, 1994

35. Lehmacher W, Wassmer G: Adaptive sample size calculations in group sequential trials. Biometrics 55:1286-1290, 1999

36. Kieser M, Bauer P, Lehmacher W: Inference on multiple endpoints in clinical trials with adaptive interim analyses. Biometrical J 41:261-277, 1999

37. Lepri AC, Smith GD, Mocroft A, et al: A practical approach to adjusting for attrition bias in

HIV clinical trials with serial marker responses. AIDS 12:1155-1161, 1998

38. Myers WR: Handling missing data in clinical trials: An overview. Drug Info J 34:525-533, 2000

39. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH E9. Statistical Principles for Clinical Trials. London, United Kingdom, European Agency for the Evaluation of Medicinal Products, 1998

40. de Jong FA, Engels FK, Mathijssen RH, et al: Medicinal cannabis in oncology practice: Still a bridge too far? J Clin Oncol 23:2886-2891, 2005

41. Hall W, Christie M, Currow D: Cannabinoids and cancer: Causation, remediation, and palliation. Lancet Oncol 6:35-42, 2005

42. Massa F, Marsicano G, Hermann H, et al: The endogenous cannabinoid system protects against colonic inflammation. J Clin Invest 113:1202-1209, 2004

43. Argiles JM, Busquets S, Lopez-Soriano FJ: Cytokines in the pathogenesis of cancer cachexia. Curr Opin Clin Nutr Metab Care 6:401-406, 2003

44. Izzo AA: Cannabinoids and intestinal motility: Welcome to CB2 receptors. Br J Pharmacol 142:1201-1202, 2004

45. Bruera E, Belzile M, Neumann C, et al: A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manage 19:427-435, 2000

46. Dahele M, Fearon KC: Research methodology: Cancer cachexia syndrome. Palliat Med 18:409-417, 2004

47. Fearon KC, Von Meyenfeldt MF, Moses AG, et al: Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: A randomised double blind trial. Gut 52:1479-1486, 2003

48. Gordon JN, Trebble TM, Ellis RD, et al: Thalidomide in the treatment of cancer cachexia: A randomised placebo controlled trial. Gut 54:540-545, 2005

49. Jatoi A, Rowland K, Loprinzi CL, et al: An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: A North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. J Clin Oncol 22:2469-2476, 2004

■ ■ ■

Acknowledgment

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Martin Schnelle	Institute for Clinical Research, Berlin, Germany (N/R)							
Marcus Reif	Institute for Clinical Research, Berlin, Germany (N/R)							
Dollar Amount Codes	(A) < $10,000	(B) $10,000-99,999	(C) ≥ $100,000	(N/R) Not Required				

Author Contributions

Conception and design: Florian Strasser, Diana Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Martin Schnelle, Marcus Reif, Thomas Cerny

Financial support: Martin Schnelle

Administrative support: Florian Strasser, Martin Schnelle, Thomas Cerny

Provision of study materials or patients: Florian Strasser, Diana Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Thomas Cerny

Collection and assembly of data: Florian Strasser, Diana Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Thomas Cerny

Data analysis and interpretation: Florian Strasser, Marcus Reif, Thomas Cerny

Manuscript writing: Florian Strasser, Diana Luftner, Thomas Ruhstaller, Marcus Reif, Thomas Cerny

Final approval of manuscript: Florian Strasser, Diana Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Martin Schnelle, Marcus Reif, Thomas Cerny