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Managing Cancer And Living Meaningfully (CALM): Randomized Feasibility Trial in Patients with Advanced Cancer

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ABSTRACT

Background: Managing Cancer And Living Meaningfully (CALM) is a brief individual psychotherapy for patients with advanced cancer. In an intervention-only phase 2a trial, CALM showed promising results, leading to the present 2b study, which introduces procedures for randomization and improved rigor in preparation for a phase 3 randomized controlled trial (RCT).

Aims: To test trial methodology and assess feasibility of a confirmatory RCT.

Design: A parallel-arm RCT (intervention vs. usual care) with 3 and 6 month follow-ups. Assessment of feasibility included rates of consent, randomization, attrition, intervention non-compliance and usual care contamination. Primary outcome: depressive symptoms (Patient Health Questionnaire-9; PHQ-9). Secondary outcomes: major depressive disorder (MDD), generalized anxiety, death anxiety, spiritual wellbeing, attachment anxiety and avoidance, self-esteem, experiential avoidance, quality of life and posttraumatic growth. Bayesian conjugate analysis was used in this low-powered setting.

Setting/participants: Sixty adult patients with advanced cancer from the Princess Margaret Cancer Centre.

Results: Rate of consent was 32%, randomization 78%, attrition 25%, non-compliance 37% and contamination 17%. There was support for potential treatment effects on: PHQ-9, Odds Ratio (OR) = 1.48, 95% Credible Interval (CRI_{.95}) (0.65, 3.38); MDD, OR = 1.56, CRI_{.95} (0.50, 4.84); attachment anxiety, OR = 1.72, CRI_{.95} (0.73, 4.03); and attachment avoidance, OR = 1.58, CRI_{.95} (0.67, 3.71). There was no support for effects on the 7 remaining secondary outcomes.

Conclusions: A phase 3 CALM RCT is feasible and should aim to detect effect sizes of $d = 0.40$, with greater attention to issues of compliance and contamination. Registration: ClinicalTrials.gov NCT02353546.

Keywords: affective symptoms, cancer, depression, palliative care, pilot trial, psychotherapy

Word Count: 3,349

INTRODUCTION

Emotional disturbances are common in patients with advanced or metastatic cancer, with anxiety peaking at the time of diagnosis and again at recurrence and with depression becoming more common with disease progression and proximity to death.^{1,2} Depression in this context may be considered a final common pathway of distress in response to the symptom burden of disease and its interaction with protective psychosocial factors, including attachment security, self-worth and spiritual wellbeing.³ In this circumstance, the threat of mortality and the progression of disease heighten fears about dependency and suffering and call into question the values that shape meaning in life.⁴

Several group therapies have been developed for patients with life threatening illness, including supportive expressive,⁵⁻⁷ cognitive existential,^{8,9} and meaning-centered¹⁰ group therapies. However, the feasibility of group therapy for many patients with metastatic cancer may be limited for a number of reasons. These include problems associated with scheduling in the context of advancing illness and medical treatments, as well as the burden for patients of absorbing the emotional distress of others, when they have not yet processed their own. Also, patients may prefer private time to discuss the personal implications of recent and tragic life-altering events that can feel overwhelming. These factors, as well as disability due to the progression of disease, may contribute to the problem of attrition that has been encountered in studies of group psychotherapy with mixed samples of patients with metastatic cancer.¹¹

More recently, a small number of evidence-based individual psychotherapies have shown benefit with patients living with advanced disease. Dignity Therapy is based on strengthening the sense of dignity at the end of life and is primarily intended for patients near or proximate to death.^{12,13} Meaning-centered individual psychotherapy seeks to improve spiritual wellbeing and the sense of meaning and purpose.^{14,15} Its modules are delivered in a standardized format and sequence and involve a combination of didactics, experiential exercises and psychotherapeutic techniques to promote exploration of meaning and its uses in coping with advanced disease.

We have developed a brief, individual, supportive-expressive psychotherapy that focuses on both the practical and psychological problems that contribute to distress in advanced cancer.¹⁶ Managing Cancer And Living Meaningfully (CALM) shares features with the therapies described above and is characterized by: targeting of patients with an expected prognosis of 12-18 months; an individualized format; focus on four broad domains of disease experience that were empirically identified in metastatic cancer; and, attention to the process of mentalization and to attachment security. Mentalization refers to the capacity to reflect on feeling states, to distinguish them from literal facts, and to accept the possibility of multiple perspectives.¹⁷ Support for mentalization within the therapeutic context may help individuals to understand the personal meaning of disease while also facing its literal reality.⁴ Attachment security, which refers to internalized expectations of emotional support from significant others and the flexible capacity to make use of it,¹⁸ has been shown to be an important mediator of distress³ and spiritual wellbeing¹⁹ in patients with advanced cancer and is a potential target of psychotherapeutic interventions.²⁰

In an intervention-only phase 2a pilot trial of 50 patients with advanced cancer, CALM was associated with reductions in depressive symptoms and death anxiety and an increase in spiritual wellbeing.²¹ These results were promising, leading to the present phase 2b pilot trial in which we have introduced procedures for randomization and improved rigor in preparation for a phase 3 confirmatory study. The purpose of this phase was to test trial methodology and assess feasibility issues for a large scale RCT.

METHODS

Trial Design

This phase 2b pilot was a parallel-arm RCT with intervention and usual care arms. Assessments were at baseline (t0), 3 months (t1) and 6 months (t2), which was the endpoint of interest. The primary outcome was depressive symptoms assessed by the Patient Health Questionnaire-9 (PHQ-9).²² Secondary outcomes were diagnosis of major depressive disorder (MDD), generalized anxiety, death anxiety, spiritual wellbeing, attachment security, self-esteem, experiential avoidance, quality of life and posttraumatic growth. Intervention participants completed a measure assessing self-reported therapeutic benefit at t1 and t2. This study was approved by the University Health Network (UHN) Research Ethics Board and registered with ClinicalTrials.gov (NCT02353546).

Participants

Participants were outpatients with advanced or metastatic cancer attending the Princess Margaret Cancer Centre, University Health Network, in Toronto, Canada. Eligibility criteria included adult age; English fluency; and a confirmed diagnosis of Stage IIIB or IV lung cancer, Stage III or IV ovarian or fallopian tube cancer, Stage IV endocrine, breast, gastrointestinal, genitourinary or gynecologic cancer, or pancreatic cancer at any stage due to the aggressiveness of this illness (all diagnoses consistent with an expected prognosis of 12-18 months). Exclusion criteria included cognitive impairment found on the Short Orientation-Memory-Concentration Test²³ administered at recruitment; and actively receiving in-hospital psychiatric or psychological treatment.

Procedure

Outpatient clinic lists were screened and patients with advanced cancer were mailed introductory letters concerning the study. Patients were recruited by research staff while attending clinic appointments. The study was described to patients who upon providing written informed consent, were randomized after completing a t0 assessment. Usual care participants were offered the option of CALM at study end.

Randomization

The randomization sequence was created by Dr. Chris Lo using a table of random digits. Simple randomization was employed with 1:1 allocation between arms. Research staff were blinded to the sequence, which was written on cards and sealed in envelopes to be opened at assignment.

Intervention

CALM is a brief, manualized, individual psychotherapy consisting of 3-6 sessions delivered over 3-6 months that addresses four empirically derived domains: symptom management and communication with health care providers, changes in self and relations with close others, sense of meaning and purpose, and concerns related to the future and mortality.^{16,21,24} CALM is individualized in that it is

tailored to the particular needs of the patient in content and process. Domains are explored with every patient but the sequence and attention to each is dependent on their salience to participants during each session. CALM domains are not standardized modules that are delivered in a set sequence, but are a framework by which therapists explore patient experience. Related to the importance of attachment security and the family as the unit of care, the participant's primary caregiver, most often the spouse or partner, adult son or daughter, is invited to join one or more sessions as deemed appropriate by therapist and patient. Caregivers did not complete any measures.

The number of sessions received is determined by the rate of reduction of distress and resolution of difficulties within each domain, and by such other factors as the patient's functional capacity and ability to attend sessions. CALM includes attention to practical needs, development of a therapeutic relationship, support for mentalization, interpretation and the joint creation of meaning, and renegotiation of attachment security. The 3-6 month time frame and the recommendation of 1 session per month was based on our team experience about the most feasible duration and frequency of sessions that would allow for alleviation of distress and improved adaptation to disease, taking into account interruptions in therapy due to scheduling difficulties, cancer treatment side effects and disease progression. Therapists aim to deliver a minimum of 3 sessions within 3 months and participants are deemed compliant with intervention when they receive this number. CALM was delivered by trained clinicians in the Department of Supportive Care at the Princess Margaret. Weekly group supervision of therapists was provided by Drs. Gary Rodin and Sarah Hales to discuss case formulation, treatment goals and appropriate CALM intervention, and to ensure treatment adherence and skill development.

Usual Care

Usual care included access to psychosocial services provided by social workers, psychologists and psychiatrists in the Department of Supportive Care. Referral at our centre occurs in approximately 33% of advanced cancer patients, of whom 66% are seen by a social worker and 33% are seen by a psychiatrist or psychologist.²⁵ Most psychosocial care is therefore provided by social workers and involves brief supportive interactions and instrumental assistance without psychotherapy. For patients referred to a psychologist or psychiatrist, care involves diagnostic consultation, treatment with pharmacotherapy if needed, and/or brief psychotherapy that is integrative in nature and may draw on cognitive behavioral, interpersonal, psychodynamic or other techniques depending on need and clinician training.

Measures

Physical symptom burden was measured using a brief version of the Memorial Symptom Assessment Scale,²⁶ assessing the severity of 28 common physical symptoms of cancer in the past week.

The primary outcome was depressive symptoms measured by the PHQ-9.²² Major depressive disorder (MDD) diagnosis was made using the depression component of the Mood Disorders and Optional Disorders Module of the Structured Clinical Interview for DSM Disorders (SCID).²⁷ SCID interviews were conducted by 3 consistent research staff, trained and monitored with monthly case-review by Dr. Madeline Li, a cancer psychiatrist blinded to randomization and PHQ-9 scores. Generalized anxiety was assessed with the Generalized Anxiety Disorder-7 (GAD-7).²⁸

Death anxiety was measured using the 15-item Death and Dying Distress Scale.²⁹ Spiritual wellbeing was measured with the 12-item Functional Assessment of Chronic Illness Therapy-Spiritual Well-being Scale.³⁰ Attachment security refers to the capacity to rely on and trust others during times of need and was assessed with the 16-item Modified Experiences in Close Relationships scale.¹⁸ The scale measures the dimensions of attachment anxiety (i.e. fear of abandonment by others) and attachment avoidance (i.e. defensive independence with minimization of distress). Self-esteem was measured using the 10-item Rosenberg Self-esteem Scale.³¹ Experiential avoidance refers to the tendency to avoid and reject negative emotions and was measured using the 10-item Acceptance and Action Questionnaire-II.³²

Quality of life was measured with the 14-item Quality of Life at the End of Life-Cancer Scale.³³ Posttraumatic growth was measured by the Posttraumatic Growth Inventory,³⁴ a 21-item scale assessing positive psychological changes (e.g. greater appreciation of life, spiritual change and relational growth) after traumatic experiences, including cancer. Therapeutic benefit from CALM was assessed with the 13-item Therapeutic Realizations Scale-Revised.³⁵ Items are rated from 0-3, where 0 refers to “no benefit”, 1 “some”, 2 “quite a bit”, and 3 “a great deal”.

Sample Size

Based on Hertzog’s guidelines for pilot work,³⁶ a total sample size of 60 was chosen as offering an acceptable trade-off between power and the dedication of resources at this phase of study, allowing for detection of only large effects equal to eta-squared of 0.14 with 90% confidence between 0.04 to 0.31.

Statistical Analyses

Data analysis was assisted by SAS/STAT software, Version 9.3.³⁷ Feasibility was assessed by rates of consent; randomization; attrition; non-compliance with intervention, defined as the percentage of CALM participants who received less than 3 sessions; and contamination of usual care, defined as the percentage of usual care participants who received 2 or more sessions with a CALM-trained therapist over the study period.

Inherent in the design of this RCT are hypotheses that intervention participants will show greater improvement relative to control participants. Traditional significance testing in a low-powered setting may be problematic and therefore a Bayesian approach was taken to investigate the likelihood of treatment effects, focusing on the t2 endpoint.^{38,39} This was a conjugate analysis using an approximate normal likelihood for the logarithm of the odds ratio (OR) as a statistical model. Study data was used to update a prior probability distribution of the log OR, yielding a posterior distribution that allows for intuitive inferences about the probability of an effect. In essence, a prior estimate of the OR is averaged with that found in the study to produce a posterior estimate for interpretation. No interim or dosage analyses were planned or conducted.

On self-reported outcomes, individuals were categorized as showing clinical improvement or not at t2 relative to baseline. Changes score thresholds indicating improvement were chosen which equated to effect sizes on the order of $d = 0.40$, consistent with the magnitude of effects found in prior research.⁴⁰ The exception was self-esteem for which a minimal 2 point raw score difference equated to $d = 0.60$.

OR's were calculated to compare the odds of improvement between arms. Concerning the SCID, analysis simply focused on the odds of depression diagnosis between arms. Attrition rates among MDD cases were examined to see whether a decrease in the odds of MDD in the intervention arm may be due to greater attrition of MDD cases in that arm relative to usual care.

Conjugate analyses were conducted on all outcomes. Skeptical priors were chosen centered on an OR of 1, i.e. no effect. For improvement outcomes, the variance of the prior distribution was set to equal the variance of the observed data at t2, essentially weighting the prior with an equivalent sample size.⁵¹ For the SCID, the prior was modeled on the baseline distribution of MDD cases. The posterior distributions were summarized by a mean estimate and 95% credible intervals. Based on the posterior distribution, we calculated the probability of a treatment effect greater than an OR of 1.25 (i.e. a 25% increase in the odds of improvement), a reasonable criterion for a clinically meaningful difference between groups.

RESULTS

Feasibility and Descriptive Statistics

Recruitment occurred from June 2011 to February 2012; 75% (237/316) of individuals were eligible for study, of whom, 32% (77/237) consented to participate, and of whom, 78% (60/77) were randomized (see Figure 1). Sample characteristics are shown in Table 1. Intervention and usual care groups were well matched, both being mostly married, female, Caucasian, and diagnosed with gastrointestinal cancer. Twenty-six percent (8/30) of intervention participants brought a primary caregiver to a session. Only 1 individual brought a caregiver twice.

Non-compliance with intervention was 37% (11/30) and contamination of usual care was 17% (5/30) (see Figure 1). The attrition rate by study end was 25% (15/60) (see Figure 1). For intervention participants, the mean t1 assessment occurred 3.83 months, SD = 0.62, after trial entry and the t2 assessment, 6.59 months, SD = 0.61. For usual care, the mean t1 assessment occurred 3.71 months, SD = 0.59, after trial entry and the t2 assessment, 6.59 months, SD = 0.57.

The change score thresholds used to identify participants who improved on self-reported outcomes are shown in Table 2. The odds of improvement and MDD diagnosis are described in Table 3.

Primary Outcome

The PHQ-9 posterior distribution is summarized in Table 4. There was support for a potential treatment effect, with 66% probability of an OR > 1.25. Intervention participants were estimated to have 1.48 times greater odds of improvement than usual care participants.

Secondary Outcomes

The posterior distributions offered support for potential effects on 3 of 10 secondary outcomes: MDD diagnosis, attachment anxiety and attachment avoidance (see Table 4).

On MDD, there was a 65% probability of an OR > 1.25. Usual care participants were estimated to have 1.56 times greater odds of MDD diagnosis than intervention participants. Note that attrition rates of MDD cases were comparable between arms. The 5 MDD cases in the intervention arm all presented at

baseline with MDD and attrition was 0% (0/5) at 3 months and 40% (2/5) at 6 months. In usual care, there were 8 MDD cases over the study period. They were all assessed at baseline and attrition was 0% (0/8) at 3 months and 38% (3/8) at 6 months.

On attachment anxiety, there was a 76% probability of an OR > 1.25. Intervention participants were estimated to have 1.72 times greater odds of improvement than usual care participants. On attachment avoidance, there was a 71% probability of an OR > 1.25. Intervention participants were estimated to have 1.58 times greater odds of improvement than usual care participants.

Therapeutic Benefit

Table 5 presents descriptive statistics on self-reported therapeutic benefit. Most item means ranged from 1 to 2 indicating mild (“some”) to moderate (“quite a bit”) benefit. The most highly rated items were the chance to unburden and express feelings and the experience of reassurance and encouragement.

DISCUSSION

The results of this pilot study support the feasibility of conducting a phase 3 RCT of CALM in patients with advanced cancer. We found that 32% of eligible individuals from a non-referred outpatient population consented to participate over a nine month recruitment period, of whom 78% were randomized. As a result of recruitment earlier in the course of disease and of more systematic follow-up, the attrition rate of 25%, was substantially less than the attrition rate of 68% observed in our previous intervention-only pilot trial.²¹

Non-compliance with intervention was comparable in both pilots, with 37% of participants receiving less than 3 sessions in this trial, compared to 42% in the earlier study.²¹ Greater accommodation in appointment scheduling, based on patient availability and timely recruitment before progressive physical decline can facilitate compliance. However, attendance at sessions is dependent on many factors, such as functional capacity, severity of physical symptoms and conflicting medical appointments or interventions that are beyond the control of the patient or the research team. Contamination of usual care was found to be present in 17%. More rigorous monitoring is needed to ensure that usual care participants referred to psychosocial services at our centre are treated by therapists who have not been exposed to CALM therapy. More detailed documentation of other psychiatric and psychosocial treatments that were received is also needed in a phase 3 trial to clarify treatment efficacy.

The most commonly reported therapeutic benefits of CALM were reassurance and the opportunity for emotional expression. These effects are consistent with the supportive-expressive foundations of CALM and its emphasis on the provision of reflective space and support within a therapeutic relationship. Most benefits were rated in the mild to moderate range. This magnitude of effect may relate to the quality of intervention, the measurement tools, and the recruitment of non-distressed individuals. Refinement of the supervision with regard to ongoing case formulation, monitoring and addressing therapeutic challenges and persistent distress, supporting mentalization, and ensuring adequate attention to all four domains may improve outcomes. The rigor of a future trial and the demonstration of benefit may also

be improved by the use of a tailored measure to assess the benefits of the intervention in relation to CALM domains and by establishing a cut-off point on the primary outcome as an entry criterion.

This pilot study was not powered to confirm treatment efficacy and therefore caution is warranted concerning the interpretation of effects. There was support for potential treatment effects on PHQ-9, with 66% chance of an OR > 1.25, and on MDD, with 65% chance of an OR > 1.25. CALM participants were estimated to have 1.48 times greater odds of improvement on PHQ-9; usual care participants were estimated to have 1.56 times greater odds of MDD compared to CALM participants. There was 76% chance of an OR > 1.25 on attachment anxiety and 71% chance of an OR > 1.25 on attachment avoidance. CALM participants were estimated to have 1.72 times greater odds of improvement on attachment anxiety and 1.58 times greater odds of improvement on attachment avoidance than usual care participants. These findings are consistent with previous research demonstrating that attachment security is responsive to psychotherapy²⁰ and with a qualitative study indicating that CALM helped participants to resolve relational problems.²⁴ Attachment security may be particularly amenable to therapeutic intervention because the threat posed by illness and death and the anticipation of increasing dependency needs heightens the salience of attachment security.^{3,4} There was no support for effects on the 7 remaining secondary outcomes, for which the probability of an OR > 1.25 was found to range from 8% to 34%. Overall, a phase 3 trial should be prepared to detect effect sizes on the order of $d = 0.40$.

Study limitations include the small sample size and its representativeness since a majority of participants were married, well-educated, English-speaking, Caucasian and female with advanced gastrointestinal cancer. The study was unblinded, which may also have affected study outcomes. Participants were not selected based on elevated distress scores, which may have limited the demonstration of benefit.

Conclusions

Phase 3 RCT's of CALM, which are needed to test efficacy, are feasible to conduct in patients living with advanced cancer. Treatment effects may be enhanced by improving compliance with intervention and by reducing contamination of usual care. Phase 3 trials of CALM should be powered to detect effect sizes of $d = 0.40$.

What is already known on this topic

Psychological distress is common in patients living with advanced cancer.

Individual psychotherapies, such as Dignity Therapy and Meaning-Centered Psychotherapy, have been shown to be of benefit in this population. The former is typically delivered close to the end of life and the latter with standardized sessions typically in a group format.

Managing Cancer And Living Meaningfully (CALM) is a brief, supportive-expressive psychotherapy that addresses practical and treatment-related issues and that supports reflection and mentalization across domains that are relevant to patients with advanced cancer.

CALM is tailored in its content and process and targets individuals with an expected prognosis of 12-18 months.

In an earlier non-randomized pilot trial, CALM was associated with reductions in depressive symptoms and death anxiety and with growth in spiritual wellbeing.

What this study adds

Evidence that: 1. A large-scale randomized controlled psychotherapy trial is feasible in patients living with advanced cancer;

2. The ability to determine treatment efficacy in a future trial may require measures to improve compliance with intervention and contamination of usual care; and

3. A phase 3 trial should be powered to detect effect sizes of $d = 0.40$.

Contributors

The study was conceived and designed by CL, SH and GR, with refinements made by AC, TP, CM, JJ, AR, RN and CZ. ML supervised SCID training and administration. Data analysis was conducted by CL. All authors contributed to drafting the manuscript, the interpretation of results, and have read and approved the final version. The guarantors are CL, SH and GR.

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Data sharing: No additional data available.

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REFERENCES

1. Li M, Boquiren VM, Lo C, et al. Depression and anxiety in supportive oncology. In: Davis M, Feyer P, Ortner P, Zimmermann C (eds) *Supportive Oncology*. Philadelphia: Elsevier, 2011, pp. 528-540.
2. Lo C, Zimmermann C, Rydall AC, et al. Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. *J Clin Oncol* 2010; 28: 3084-3089.
3. Rodin G, Lo C, Mikulincer M, et al. Pathways to distress: the multiple determinants of depression, hopelessness, and desire for hastened death in metastatic cancer patients. *Soc Sci Med* 2009; 68: 562-569.
4. Rodin G. Individual psychotherapy for the patient with advanced disease. In: Chochinov H, Breitbart W (eds) *Handbook of Psychiatry in Palliative Medicine*. London: Oxford University, 2009, pp. 443-453.
5. Spiegel D, Bloom JR and Yalom I. Group support for patients with metastatic cancer: a randomized outcome study. *Arch Gen Psychiatry* 1981; 38: 527-533.
6. Classen C, Butler LD, Koopman C, et al. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. *Arch Gen Psychiatry* 2001; 58: 494-501.
7. Bordeleau L, Szalai JP, Ennis M, et al. Quality of life in a randomized trial of group psychosocial support in metastatic breast cancer: overall effects of the intervention and an exploration of missing data. *J Clin Oncol* 2003; 21: 1944-1951.
8. Kissane DW, Bloch S, Smith GC, et al. Cognitive-existential group psychotherapy for women with primary breast cancer: a randomised controlled trial. *Psychooncology* 2003; 12: 532-546.
9. Kissane DW, Love A, Hatton A, et al. Effect of cognitive-existential group therapy on survival in early-stage breast cancer. *J Clin Oncol* 2004; 22: 4255-4260.
10. Breitbart W, Gibson C, Poppito SR, et al. Psychotherapeutic interventions at the end of life: a focus on meaning and spirituality. *Can J Psychiatry* 2004; 49: 366-372.
11. Applebaum AJ, Lichtenthal WG, Pessin HA, et al. Factors associated with attrition from a randomized controlled trial of meaning-centered group psychotherapy for patients with advanced cancer. *Psychooncology* 2012; 21: 1195-1204.
12. Chochinov HM, Hack T, Hassard T, et al. Dignity Therapy: a novel psychotherapeutic intervention for patients near the end of life. *J Clin Oncol* 2005; 23: 5520-5525.

13. Juliao M, Barbosa A, Oliveira F, et al. Efficacy of dignity therapy for depression and anxiety in terminally ill patients: Early results of a randomized controlled trial. *Palliat Support Care* 2013; 11: 481-489.
14. Breitbart W, Poppito S, Rosenfeld B, et al. Pilot randomized controlled trial of individual meaning-centered psychotherapy for patients with advanced cancer. *J Clin Oncol* 2012; 30: 1304-1309.
15. Thomas LP, Meier EA and Irwin SA. Meaning-Centered Psychotherapy: a form of psychotherapy for patients with cancer. *Curr Psychiatry Rep* 2014; 16: 488.
16. Hales S, Lo C and Rodin G. *Managing Cancer And Living Meaningfully (CALM) treatment manual: an individual psychotherapy for patients with advanced cancer*. ©2010, Princess Margaret Hospital, University Health Network, Toronto, Canada.
17. Fonagy P, Gergely G, Jurist E, et al. *Affect Regulation, Mentalization, and the Development of the Self*. New York: Other Press, 2002.
18. Lo C, Walsh A, Mikulincer M, et al. Measuring attachment security in patients with advanced cancer: psychometric properties of a modified and brief Experiences in Close Relationships scale. *Psychooncology* 2009; 18: 490-499.
19. Lo C, Zimmermann C, Gagliese L, Li M, Rodin G. Sources of spiritual well-being in advanced cancer. *BMJ Support Palliat Care* 2011; 1: 149-153.
20. Kirchmann H, Steyer R, Mayer A, et al. Effects of adult inpatient group psychotherapy on attachment characteristics: an observational study comparing routine care to an untreated comparison group. *Psychother Res* 2012; 22: 95-114.
21. Lo C, Hales S, Jung J, et al. Managing Cancer And Living Meaningfully (CALM): phase 2 trial of a brief individual psychotherapy in advanced cancer. *Palliat Med* 2014; 28: 234-242.
22. Kroenke K, Spitzer RL and Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16: 606-613.
23. Katzman R, Brown T, Fuld P, et al. Validation of a short orientation-memory-concentration test of cognitive impairment. *Am J Psychiatry* 1983; 140: 734-739.
24. Nissim R, Freeman E, Lo C, et al. Managing Cancer and Living Meaningfully (CALM): a qualitative study of a brief individual psychotherapy for individuals with advanced cancer. *Palliat Med* 2012; 26: 713-721.

25. Ellis J, Lin J, Walsh A, et al. Predictors of referral for specialized psychosocial oncology care in patients with metastatic cancer: the contributions of age, distress and marital status. *J Clin Oncol* 2009; 27: 699-705.
26. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer* 1994; 30A: 1326-1336.
27. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders- Patient Edition (SCID-I/P, 1/2010 revision)*. New York, NY: New York State Psychiatric Institute, 2010.
28. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; 166: 1092-1097.
29. Krause S, Rydall A, Hales S, et al. Initial validation of the Death and Dying Distress Scale for the assessment of death anxiety in advanced cancer. *J Pain Symptom Manage*. 2015; 49: 126-134.
30. Peterman AH, Fitchett G, Brady MJ, et al. Measuring spiritual well-being in people with cancer: the Functional Assessment of Chronic Illness Therapy – Spiritual Well-Being Scale (FACIT-Sp). *Ann Behav Med* 2002; 24: 49-58.
31. Rosenberg M. *Society and the Adolescent Self-Image*. Middletown, England: Wesleyan University Press, 1989.
32. Bond FW, Hayes SC, Baer RA, et al. Preliminary psychometric properties of the Acceptance and Action Questionnaire-II: a revised measure of psychological inflexibility and experiential avoidance. *Behav Ther* 2011; 42: 676-688.
33. Lo C, Burman D, Swami N, et al. Validation of the QUAL-EC for assessing quality of life in patients with advanced cancer. *Eur J Cancer* 2011; 47: 554-560.
34. Tedeschi RG and Calhoun LG. The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. *J Traumatic Stress* 1996; 9: 455-471.
35. Kolden GG, Strauman TJ, Gittleman M, et al. The Therapeutic Realizations Scale-Revised (TRS-R): psychometric characteristics and relationship to treatment process and outcome. *J Clin Psychol* 2000; 56: 1207-1220.
36. Hertzog MA. Considerations in determining sample size for pilot studies. *Res Nurs Health* 2008; 31: 180-191.
37. SAS Institute Inc. *SAS/STAT, version 9.3, SAS System*. ©2002-2010, Cary, NC, USA.

38. Spiegelhalter DJ, Abrams KR and Myles JP. *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. Chichester, England: Wiley, 2004, pp. 49-78.
39. Gurrin LC, Kurinczuk JJ and Burton PR. Bayesian statistics in medical research: an intuitive alternative to conventional data analysis. *J Eval Clin Pract* 2000; 6: 193-204.
40. Akechi T, Okuyama T, Onishi J, et al. Psychotherapy for depression among incurable cancer patients. *Cochrane Database Syst Rev* 2008 Apr 16; 2: CD005537.

Table 1. Baseline characteristics (N=60).

Variable	Usual care (n=30) M (SD) or % (frequency)	CALM (n=30) M (SD) or % (frequency)
Age in years	56.62 (11.36)	55.37 (12.13)
Female	73% (22)	67% (20)
Caucasian	90% (27)	93% (28)
Married/common law	67% (20)	67% (20)
Living alone	20% (6)	20% (6)
Post-secondary education	80% (24)	87% (26)
<i>Annual household income</i>		
<\$30,000	13% (4)	10% (3)
\$30,000 – \$59,999	17% (5)	27% (8)
\$60,000 – \$99,999	27% (8)	20% (6)
\$100,000+	30% (9)	27% (8)
Did not respond	13% (4)	17% (5)
Years since cancer diagnosis	2.39 (2.86)	2.69 (2.75)
<i>Disease site</i>		
Breast	20% (6)	7% (2)
Endocrine	0% (0)	3% (1)
Gastrointestinal	37% (11)	57% (17)
Genitourinary	10% (3)	13% (4)
Gynecological	27% (8)	17% (5)
Lung	7% (2)	3% (1)
Physical symptom count	12.50 (4.08)	11.57 (5.20)
Physical symptom severity	0.77 (0.33)	0.72 (0.42)
PHQ-9	8.03 (4.46)	7.27 (5.38)
MDD ^a	14% (4)	18% (5)
GAD-7	5.63 (4.90)	4.97 (4.15)
Death anxiety	34.73 (18.58)	32.38 (21.86)
Spiritual wellbeing	30.00 (9.19)	30.48 (9.72)
Attachment anxiety	18.63 (6.98)	23.57 (9.84)
Attachment avoidance	20.73 (9.73)	25.26 (9.04)
Self-esteem	33.37 (4.50)	32.03 (5.84)
Experiential avoidance	27.43 (8.71)	31.03 (11.72)
Quality of life	47.83 (8.40)	47.47 (9.56)
Posttraumatic growth	53.10 (19.86)	57.43 (23.46)

M = mean. SD = standard deviation.

^aUsual care (n = 29); CALM (n = 28).

Table 2. Change score thresholds for clinical improvement.

Outcome	Δ_{t2-t0} threshold	Pooled SD of Δ_{t2-t0}	Effect size d_{t2-t0}
PHQ-9	-2	5.11	0.39
GAD-7	-2	5.29	0.38
Death anxiety	-7	16.35	0.43
Spiritual wellbeing	+2	5.87	0.34
Attachment anxiety	-3	6.65	0.45
Attachment avoidance	-3	6.85	0.44
Self-esteem	+2	3.32	0.60
Experiential avoidance	-3	7.15	0.42
Quality of life	+3	6.71	0.45
Posttraumatic growth	+8	20.53	0.39

Δ_{t2-t0} threshold = change score threshold. $t0$ = baseline assessment. $t2$ = 6 month assessment. SD = standard deviation.

Table 3. Odds of improvement and depression diagnosis.

	Usual care	CALM	CALM: Usual care	Usual care	CALM	CALM: Usual care
Outcome	Odds of improve- ment at t1	Odds of improve- ment at t1	Odds ratio at t1	Odds of improve- ment at t2	Odds of improve- ment at t2	Odds ratio at t2
PHQ-9	7:19	14:10	3.80	10:11	16:8	2.20
GAD-7	12:12	9:13	0.69	10:11	10:14	0.79
Death anxiety	11:13	10:12	0.98	10:11	8:15	0.59
Spiritual wellbeing	11:13	13:9	1.71	14:7	12:12	0.50
Attachment anxiety	6:18	14:8	5.95	6:15	13:11	2.95
Attachment avoidance	9:15	8:14	0.95	6:15	12:12	2.50
Self-esteem	6:18	6:16	1.13	8:13	5:19	0.43
Experiential avoidance	11:13	12:10	1.42	11:10	9:15	0.55
Quality of life	10:14	5:17	0.42	10:11	12:12	1.10
Posttraumatic growth	8:16	5:17	0.59	10:11	9:15	0.66
			Usual care: CALM			Usual care: CALM
	Odds of diagnosis at t1	Odds of diagnosis at t1	Odds ratio at t1	Odds of diagnosis at t2	Odds of diagnosis at t2	Odds ratio at t2
MDD	5:21	2:22	2.62	3:16	1:22	4.13

Note. Odds are presented as the frequency of cases showing improvement vs. no improvement, or of cases with MDD diagnosis vs. no MDD diagnosis. Odds ratios for improvement compare CALM vs. Usual care, whereas odds ratios for MDD compare Usual care vs. CALM.

t1 = 3 month assessment. t2 = 6 month assessment.

Table 4. Posterior distributions.

	CALM: Usual Care		
Outcome	Mean OR for improvement	95% Credible interval	Probability of OR > 1.25
PHQ-9	1.48	0.65, 3.38	0.66
GAD-7	0.89	0.39, 2.01	0.21
Death anxiety	0.77	0.33, 1.77	0.13
Spiritual wellbeing	0.71	0.31, 1.63	0.09
Attachment anxiety	1.72	0.73, 4.03	0.76
Attachment avoidance	1.58	0.67, 3.71	0.71
Self-esteem	0.66	0.27, 1.62	0.08
Experiential avoidance	0.74	0.33, 1.69	0.11
Quality of life	1.05	0.47, 2.36	0.34
Posttraumatic growth	0.81	0.36, 1.85	0.15
	Usual care: CALM		
	Mean OR for diagnosis	95% Credible interval	Probability of OR > 1.25
MDD	1.56	0.50, 4.84	0.65

Note. Odds ratios for improvement compare CALM vs. Usual care, whereas odds ratios for MDD compare Usual care vs. CALM.

OR = odds ratio.

Table 5. Self-reported therapeutic benefit.

Item	t1 M (SD) (n=21)	t2 M (SD) (n=20)
A chance to let go and express feelings	1.90 (1.09)	2.05 (0.89)
Hope: a feeling that things can work out	1.33 (0.97)	1.50 (0.83)
Help in talking about what was really troubling me	1.43 (1.16)	1.75 (0.85)
Relief from tensions or unpleasant feelings	1.14 (1.01)	1.60 (0.99)
More understanding of reasons behind my behavior and feelings	1.33 (1.11)	1.60 (0.99)
Reassurance and encouragement about how I'm doing	1.81 (0.93)	1.75 (0.97)
Confidence to try to do things differently	1.43 (0.98)	1.35 (1.04)
Ideas for better ways of dealing with people and problems	1.14 (1.01)	1.50 (1.00)
Better self-control over my moods and actions	0.90 (0.94)	1.15 (0.81)
Increased awareness that thoughts and/or feelings experienced now are similar to those in the past ^a	1.19 (1.03)	1.37 (0.76)
Increased awareness that reactions and behaviors toward someone now are similar to reactions and behaviors towards others in the past ^{a,b}	1.00 (0.86)	1.05 (0.91)
A chance to try out or practice a new skill or way of behaving	0.86 (0.96)	0.90 (0.97)
Education: information about symptoms, problems, or people	1.29 (1.10)	1.15 (1.04)
Total score	16.79 (10.23)	18.69 (8.82)

M = mean. SD = standard deviation. t1 = 3 month assessment. t2 = 6 month assessment.

^at2 (n=19). ^bt1 (n=20).

Figure 1. Patient flow diagram.