PROTOCOL TITLE: A communication-based intervention for advanced cancer patient-caregiver dyads to increase engagement in advance care planning and reduce caregiver burden

PRINCIPAL INVESTIGATOR: Dr. Megan Shen, Fred Hutchinson Cancer Center

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BACKGROUND

Prognostic understanding is vital to advanced cancer patients' ability to make informed treatment decisions and receive end-of-life (EOL) care consistent with their preferences. Advanced cancer patients who have an accurate prognostic understanding are more likely to engage in advance care planning (ACP) prefer comfort over aggressive care, and receive goal-concordant care. These patients are less likely to receive futile aggressive EOL care, a notable relationship given robust evidence that aggressive EOL care does not increase survival but is associated with poor patient quality of life and caregiver bereavement adjustment. Yet, nearly half of advanced cancer patients do not recognize they are terminally ill. Caregivers play an integral role in patients' care and decision-making and often have a more accurate understanding of the terminal nature of the patient's illness than the patient (accurate caregivers: 83.4% vs. accurate patients: 58.0%). The importance of integrating caregivers into ACP has been acknowledged, yet few interventions include them. Nearly two thirds (65%) of caregivers of advanced cancer patients report experiencing communication problems, including avoiding communication about emotionally distressing topics (e.g., fears of treatment futility). The emotional distress associated with these topics exacerbates this avoidance and leads to patient-caregiver disagreement about the patient's prognosis (up to 77% of dyads disagree). Further, caregivers with unmet needs for communication with the patient report higher burden. Our pilot work highlights the importance of patient and caregiver understanding of the patient's prognosis. In our analyses, advanced cancer patient-caregiver dyads who had an accurate understanding of the patient's prognosis were more likely to engage in ACP and prefer comfort care over aggressive care than patient-caregiver dyads in which one or both members had an inaccurate prognostic understanding. These findings indicate that promoting accurate patient-caregiver prognostic understanding is critical to improving advanced cancer patient and caregiver outcomes, such as increasing engagement in ACP and receipt of goal-concordant care and reducing caregiver burden and receipt of futile aggressive EOL care. Inadequate communication skills and distress associated with discussing prognosis are barriers to dyads' ability to reach a shared accurate understanding of the patient's illness. For instance, 46% of patients in one study mentioned relationship concerns surrounding discussing ACP with family and friends (e.g., concern about burdening others) as a major barrier to engaging in ACP. An intervention that improves patients' and caregivers' ability to communicate about the patient's illness, while managing associated distress, is critical to improving patient-caregiver shared accurate prognostic understanding and engagement in ACP. Investigators' experience: Drs. Trevino and Shen have unique yet complementary areas of expertise in the domain of EOL care research and an established working relationship. Dr. Trevino's expertise in distress management and psychosocial interventions puts her in a strong position to conduct this work, which is grounded in psychological and distress management theories. Dr. Shen's expertise in social psychological theory and health communication will inform the communication components of the intervention and their grounding in social psychological theory. Prior work by Drs. Prigerson and Maciejewski (Co-Is) highlights the need for ACP, the influence of caregivers on EOL decision-making, and the negative impact of aggressive EOL care on patients and caregivers. In our team's NCI-funded cohort study (Coping with Cancer 1, CwC1, 2002-2008, PI: Prigerson), advanced cancer patients and caregivers reported accurate understanding of the patient's life expectancy (≤ 6 months) in only 9.6% of dyads (total n=178). Patients in these dyads were more likely to have identified a health care proxy (OR=10.74, p=.02) and completed a living will (OR=6.00, p=.02) and DNR order (OR=10.80, p<.01) than dyads with inaccurate prognostic understanding. In our more recent cohort of advanced cancer patients and caregivers (NCI-funded CwC2, 2010-2015), dyads (n=101) with an accurate terminal illness understanding were most likely to have a completed patient DNR order (65.4%) compared to dyads in which one (53.6%) or both (21.0%) members had an inaccurate prognostic understanding, (p=.028). In the combined sample (CwC1&2), the interactive effect of patients and caregivers having accurate prognostic understanding predicted DNR order completion beyond individual

patient and caregiver understanding (p=.02). Improving both patients' and caregivers' prognostic understanding is critical for increasing ACP engagement.

Despite the importance of illness understanding, nearly half of advanced cancer patients do not understand their illness is terminal and patients and caregivers often have different views of the patient's prognosis. When patients and caregivers share an accurate understanding of the patient's illness, patients are more likely to document their care preferences. This documentation is associated with receipt of less aggressive care that is consistent with patients' preferences, better patient quality of life, and less caregiver distress. The ability of patients and caregivers to communicate about the patient's illness is influenced by the difficult emotions often associated with these conversations. Thus, tools are needed to help patients and caregivers manage the distress that can interfere with effective communication about the patient's illness.

The proposed study will test an intervention to improve patients' and caregivers' ability to manage difficult emotions and communicate about the patient's illness. This intervention has the potential to reduce patient and caregiver distress and improve patient and caregiver quality of life, shared understanding of the patient's illness, and patients' and caregivers' ability to discuss, identify, and document patients' treatment preferences. The intervention is designed to minimize burden to patients, caregivers, and healthcare institutions to allow for easy integration into clinical practice. Given the high levels of emotional distress and important treatment decisions faced by cancer patients and caregivers, this intervention has the potential to significantly improve patients' care and patients' and caregivers' quality of life.

STUDY DESIGN

Aims, research questions, and hypotheses:

The objective of the proposed study is to develop and pilot test an intervention that improves patient and caregiver prognostic understanding (terminal nature of illness, life-expectancy) using theoretically grounded techniques of distress tolerance (inhibitory learning theory) and communication skills (cognitive-social processing theory). This objective will be met using a mixed-methods approach across three specific aims: Aim 1: To develop an intervention to improve advanced cancer patients' and caregivers' prognostic understanding using communication (validation of fear) and distress management (deep breathing) techniques. Aim 2: To evaluate the feasibility and acceptability of the patient-caregiver communication-based intervention among advanced cancer patients and their caregivers. Hypothesis 2a: To evaluate feasibility, greater than or equal to70% of participants will meet the benchmark for feasibility defined by participant retention and adherence to the intervention. Hypothesis 2b: To evaluate acceptability, greater than or equal to 70% of participants will meet the benchmark for acceptability defined by responses on self-report measures of perceived helpfulness, satisfaction, and impact. Aim 3: To test the preliminary efficacy of the intervention on patients' and caregivers' prognostic understanding (primary outcome); completion of a DNR order, living will, and health care proxy; psychological distress; communication outcomes). Hypothesis 3: We hypothesize that the intervention will improve patients' and caregivers' prognostic understanding and communication quality; increase completion of DNR/proxy/living wills and receipt of goal-concordant care; and reduce distress, caregiver burden, and receipt of aggressive futile care. The current intervention consists of seven 45-minute telephone-delivered sessions. For Aim 1, we will collect feedback from advanced cancer patients and their caregivers (n=10 dyads) and psychosocial experts (n=10) to improve and refine the intervention. For Aims 2 and 3, we will pilot test the intervention with n=30 patient-caregiver dyads and assess outcomes at baseline, post-intervention, and three months later. Study Design Overview: To achieve Aim 1, we will let our developed preliminary intervention materials with advanced cancer

patients, their caregivers, and experts. This feedback will be used to modify the intervention. To achieve Aims 2-3, we will examine the feasibility, acceptability, and preliminary efficacy of the intervention for improving patient-caregiver prognostic understanding, completion of ADs, distress, communication quality, caregiver burden, and receipt of goal-concordant and aggressive futile EOL care.

The preliminary intervention materials described here will provide dyads and stakeholders with information on which to provide feedback (Aim 1). We will modify these intervention materials based on data collected from participants in Aim 1. The current intervention consists of six 45- minute sessions conducted over the telephone using patient and caregiver workbooks and corresponding interventionist manuals (see Table 1). Telephone delivery was selected to minimize the burden to patients and caregivers associated with attending in-person appointments and to minimize the use of institutional resources. Two sessions (Sessions 1 and 3) will be conducted individually; the remaining sessions will be conducted together (patient, caregiver, and interventionist). This combined structure of individual and dyadic sessions is consistent with prior dyadic interventions for patients with life-limiting disease and their caregivers. The interventionist will be a master's-level licensed social worker. Each session will include didactic instruction, in-session practice of new techniques with the interventionist and/or partner, and between-session exercises to facilitate skill development and application. Patient and caregiver workbooks will support this process by providing readable instructions, images, and worksheets to promote intervention engagement.
Session topics will include:

(a) Distress management (Sessions 1 and 2). Strategies for coping with distress are taken from cognitive-behavioral therapy and coping interventions effective in cancer patients. Behavioral strategies will include deep breathing and relaxation techniques. These strategies reduce the physiological arousal (e.g., rapid heart rate) associated with elevated distress. In addition to written instructions on engaging in these strategies, patients and caregivers will be provided with audio recordings that guide them through each strategy. Cognitive strategies will focus on cognitive restructuring. Cognitive restructuring techniques identify thoughts that are inconsistent with reality (i.e., cognitive errors; e.g., "I should be able to handle these decisions on my own.") and replace these thoughts with more realistic interpretations (e.g., "These decisions are difficult and discussing them with others is important."). Errors in thinking can exacerbate distress levels which generates additional cognitive errors, creating a cycle of progressively increasing distress. Participants will be provided with information on common cognitive errors (e.g., black- and-white thinking, should statements) and with strategies for identifying cognitive errors in their own thinking and replacing these errors with more realistic thoughts.

In Session 1 (individual), patients and caregivers will identify the strategies they typically use to cope with distress and will discuss the effectiveness of these strategies. This discussion will identify patients' and caregivers' unique coping strategies. Patients and caregivers will then learn about the distress management techniques described above and will select strategies to practice prior to the next session. The therapist will assist the patient/caregiver in creating a plan for distress management that integrates new techniques with previously used effective coping strategies, allowing the intervention to be tailored for differences in preferred coping strategies across individuals. In Session 2 (dyad), patients and caregivers will discuss similarities and differences in their coping responses to distress. This discussion will allow dyads to reflect on the effectiveness of individual and shared coping strategies, share their preferred distress management techniques with each other, and identify ways to support each other's distress management attempts.

(b) Communication skills (Sessions 3 and 4). Communication strategies are taken from

Gottman's recommendations for couple communication and best practices for communicating in medical contexts which highlight basic communication skills of acknowledgment, validation, expressing empathy, asking open-ended questions, and verbalizing one's feelings with "I" statements (e.g., "When we talk about your treatment not working, I feel worried."). Dyads will be guided in how to acknowledge and validate the worries, concerns, and fears of their partner surrounding the patient's prognosis as well as learning how to verbalize their own.

In Session 3 (individual), patients and caregivers will learn how to identify their concerns regarding treatment options and advance care planning. Namely, each dyad member will identify which treatment options they believe are available, their concerns about these options, and their understanding of the potential association with non-curative treatment and/or death and dying. This will be done individually to create a safe space for processing (free of the other dyad member) and to facilitate formulation of their communication of these concerns to the other dyad member. In Session 4 (dyad), patients and caregivers will discuss their current style of communicating with each other. This discussion will provide dyads with an opportunity to reflect on effective and ineffective components of their communication style and will provide the interventionists with information on the dyad's baseline communication skills. They will then engage in an interventionist-guided discussion in which they express their worries and fears about treatment options and prognosis to the other dyad member. The interventionist will provide guidance regarding the application of previously discussed communication and stress management techniques to promote effective conversation about these difficult topics.

(c) Guided review of prognostic information (Sessions 3 and 5). Cognitive restructuring techniques will be used to examine patients' and caregivers' assumptions about and interpretation of prognostic information previously provided by the patients' oncologist.[47] For example, in a pilot qualitative study examining communication about ACP (PI: Shen) a patient stated, "My doctor told me there's nothing more we can do. But I'm going to fight this and beat this cancer." Using cognitive restructuring techniques, the interventionist could say, "What do you think the doctor meant when he said, 'there's nothing more we can do'? There are many ways to fight cancer. What do you mean by 'fight this cancer'?" Questions such as this combined with support to utilize previously learned distress management and communication techniques will facilitate an accurate shared understanding of the patients' prognosis.

Session 3 (individual) will provide patients and caregivers the opportunity to discuss their understanding of the patient's prognosis separate from the other dyad member. In Session 5 (dyad), patients and caregivers will engage in a conversation about the patient's prognosis using the communication skills presented in Sessions 3 and 4 with the support of the interventionists. Study interventionists will utilize cognitive restructuring techniques in both sessions to identify and challenge cognitive distortions related to the patient's prognosis.

(d) Intervention review and future plan (Session 6). The final session will consist of a review of topics covered in the intervention and development of a plan for managing future difficult conversations about the patients' illness and treatment. The purpose of this plan is to improve participants' ability to respond effectively to future difficult conversations as they occur and to improve participants' confidence in their ability to manage these conversations.

Sample Recruitment:
Patients and caregivers will be recruited from WCM. Experts will be recruited through relevant professional societies (e.g., American Psychosocial Oncology Society) and the professional networks

(e.g., Cancer Support Community) of study team members. For Aim 1, n=10 patient-caregiver dyads and n=10 psychosocial oncology experts will be recruited. For Aims 2 and 3, n=30 advanced cancer patient- caregiver dyads will be enrolled, consistent with the recommendations of the Stage Model of Behavioral Therapies Research for evaluation of feasibility and clinically significant change. Sampling and recruitment procedures outlined here have been used for similar studies (e.g., CwC I, II, and III) with recruitment rates of 70%. The proposed recruitment procedures for experts have been successfully used in a similar intervention development study (K23 AG048632, PI: Trevino).

Proposed analyses:

Aim 1. Data coding and analysis will be informed by a responsive interviewing model in which data units, or "blocks of information" are combined based on the theme they represent. Trained raters will independently review the transcripts and identify passages that include suggestions for modifications to the intervention. Raters will then organize these passages into categories reflecting single themes. Research team members will discuss these themes and make revisions until consensus is reached on the themes of the interviews. The themes identified in this analysis will inform modifications to the intervention.

Aim 2. Feasibility and acceptability will be examined by conducting frequency and descriptive statistics (i.e., mean, median, standard deviation) for enrollment rates, number of sessions completed, number of weeks required to complete the intervention, and Likert-scale items assessing satisfaction with the intervention and perceived helpfulness. We will conduct qualitative analyses on the open-ended questions as in Aim 1. Benchmarks: The benchmark for feasibility is >=60% of screened eligible dyads enroll in the study. Further, >=70% of dyads who enroll in the study will complete 75% of the intervention sessions. For acceptability, >=70% of dyads will have an average score of greater than or equal to 2 on Likert scale items assessing perceived acceptability of 'moderately' (2) to 'very' (4) acceptable on a 0-4 scale.

Aim 3. Aim 3 will be addressed using a pre-post design. To account for the non-independence of the dyadic nature of the data (i.e., patients' and caregivers' ratings are expected to be correlated),54,55 we will use generalized linear mixed modeling (GLMM) for continuous and binary/dichotomous outcomes. A post-versus-pre- difference will be sought to estimate the rate of increase of dyads pre/post to determine the degree to which the communication-based intervention is likely to improve patient and caregiver outcomes in: patients' and caregivers' accurate prognostic understanding, engagement in ACP, completion of ADs, receipt of goal- concordant care, healthcare utilization rates, psychological distress, communication quality, and caregiver burden. Missing data. To reduce missing data, study staff will conduct interviews rather than relying on written self-reports. After attempts are made to reduce the amount of missing data, all remaining data will be assessed for missingness (e.g., random or non-random). Based on these results, the appropriate imputation methods will be used to handle missing data. Due to the ill nature of this population, it is estimated that some data will be missing not at random due to mortality of patients. As such, proper methods will be taken to deal with this data. Because this is a pilot study, sample sizes were determined based on prior recommendations for pilot pre-/post- intervention designs. Although this study will not be sufficiently powered to detect efficacy, it will allow for testing of feasibility, acceptability, and preliminary efficacy.

INCLUSION AND EXCLUSION CRITERIA

Patient eligibility requirements: (1) diagnosis of poor prognosis advanced cancer defined as locally advanced or metastatic cancer (e.g., pancreaticobiliary, esophagogastric, hepatocellular carcinoma,

lung, or gynecological cancer) and/or disease progression following at least first line chemotherapy; (2) ability to provide informed consent; (3) identification of an informal caregiver; and (4) oncologist reported discussion of prognosis with the patient and/or caregiver. These criteria have been successfully used in prior research by our study team to identify patients with a prognosis of 6 months or less to live. Caregiver eligibility requirements: (1) the person the patient indicates provides their informal (unpaid) care; (2) English speaking; and (3) able to provide informed consent. Expert eligibility requirements (Aim1 only): (1) current clinical practice and/or research with advanced cancer patients and; (2) a history of 5+ years working with advanced cancer patients. Experts across disciplines (e.g., social work, psychology) will be enrolled.

Patient exclusion criteria: (1) not fluent in English; (2) severely cognitively impaired (Short Portable Mental Status Questionnaire scores of < 6); (3) too ill or weak to complete the interviews (as judged by the interviewer); (4) receiving hospice at the time of enrollment; (5) younger than age 18; (6) deemed psychologically inappropriate for the study by their treating oncologist. To help guide referring physicians, a guide has been compiled to help define who could be considered psychologically inappropriate. This could include: a patient being too distressed by their current diagnosis, prognosis, or treatment regimen and likely to have that distress exacerbated by being approached for this study. Additional exclusion criteria include: (7) reports alcohol abuse or dependence; (8) reports abuse or dependence of another drug (like cocaine or heroin); (9) meets diagnostic criteria for a severe psychiatric disorder, including bipolar disorder, schizophrenia, or other psychotic disorders; and (10) states that they currently endorse suicidality, including a plan and intent to attempt a suicide. Patient-caregiver dyads in which both members have an accurate understanding of prognosis (terminal status and life-expectancy) will be excluded due to the lack of need for an intervention.

DATA AND SAFETY MONITORING PLAN

The Common Terminology Criteria for Adverse Events (CTCAE) of the U.S. Department of Health and Human Services will be used to identify and grade adverse events to the WCM IRB and the NIH (study program officer is Dr. Sylvia Chou).

The NIH program officer for this study. All adverse events noted by study staff will be discussed with the MPIs or designee and reported within 24 hours of discovery by study staff to IRB. Included in this report will be the date, time, and type of adverse event as well as how it was handled. The MPIs are required to report adverse events to the Institutional Review Board (IRB) on an ongoing basis. This will include a report of the first 5 subjects as well as the specified continual reporting of adverse as they arise. In addition, yearly IRB renewal submissions require detailed adverse event reporting. Adverse events are also reported as part of the progress reports in the non- competitive and competitive renewals for the NIH. All study staff will complete the NIH required training in participation and conduct of studies that involve human subjects. If study staff discover any untreated physical conditions, they will refer participants to appropriate treatment immediately. Some participants will be receiving active cancer treatment at the time of study participation; therefore, fluctuations in cancer-related symptoms will not be considered adverse events. The MPIs will discuss safety concerns, adverse events, participant complaints and, if any, protocol violations with co-investigators. These meetings will be used to determine if any additional procedures are needed to augment data and safety monitoring.

This study does not involve the use of experimental medications or devices

Because this is a pilot trial, we do not plan to conduct interim data analyses except for preliminary analyses prepared for NIH.

A DSMB was not required by the NIH for this study.