Evaluating if an Advance Care Planning Intervention Promotes Do-Not-Resuscitate Orders by Facilitating Accurate Prognostic Awareness

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ABSTRACT

Background: Issuing do-not-resuscitate (DNR) orders has seldom been an outcome in randomized clinical trials of advance care planning (ACP) interventions. The aim of this study was to examine whether an ACP intervention facilitating accurate prognostic awareness (PA) for patients with advanced cancer was associated with earlier use of DNR orders. **Patients and Methods:** Participants (n=460) were randomly assigned 1:1 to the experimental and control arms, with 392 deceased participants constituting the final sample of this secondary analysis study. Participants in the intervention and control arms had each received an intervention tailored to their readiness for ACP/prognostic information and symptom-management education, respectively. Effectiveness in promoting a DNR order by facilitating accurate PA was determined by intention-to-treat analysis using multivariate logistic regression with hierarchical linear modeling. **Results:** At enrollment in the ACP intervention and before death, 9 (4.6%) and 8 (4.1%) participants and 168 (85.7%) and 164 (83.7%) participants in the experimental and control arms, respectively, had issued a DNR order, without significant between-arm differences. However, participants in the experimental arm with accurate PA were significantly more likely than participants in the control arm without accurate PA to have issued a DNR order before death (adjusted odds ratio, 2.264; 95% CI, 1.036–4.951; $P=.041$). Specifically, participants in the experimental arm who first reported accurate PA 31 to 90 days before death were significantly more likely than their counterparts in the control arm who reported accurate PA to have issued a DNR order in the next wave of assessment (adjusted odds ratio, 13.365; 95% CI, 1.989–89.786; $P=.008$). Both arms issued DNR orders close to death (median, 5–6 days before death). **Conclusions:** Our ACP intervention did not promote the overall presence of a DNR order. However, our intervention facilitated the issuance of DNR orders before death among patients with accurate PA, especially those who reported accurate PA 31 to 90 days before death, but it did not facilitate the issuance of DNR orders earlier than their counterparts in the control arm. ClinicalTrials.gov Identification: NCT01912846

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Background

Patients with advanced cancer who receive cardiopulmonary resuscitation (CPR) have much worse short- and long-term outcomes than those without (advanced) cancer who receive CPR, a difference that has persisted over several decades.^{1,2} Moreover, patients with cancer poorly understand and overestimate the efficacy of CPR.^{3,4} Even more worrisome, high-intensity end-of-life (EoL) care may not be valued and welcomed by seriously ill patients with cancer,⁵ preventing the achievement of value-concordant EoL care.⁶ Issuing a do-not-resuscitate (DNR) order, which should not be the sole outcome of advanced care planning (ACP) for EoL care,⁷ is championed as a way to extend patient autonomy in healthcare decisions when they are incapacitated at EoL.

Although DNR orders are increasingly used by patients with advanced cancer,^{1,2} physicians do not discuss code status with most patients upon hospital admission, neglecting patients' preference to forgo CPR.⁸ DNR orders are typically issued close to death.^{1,9–16} No DNR order or a late one can signal suboptimal physician–patient EoL care communication, leading to more life-sustaining treatments (LSTs)^{10,14,17,18} and poor EoL care quality.^{17–19}

Timely, adequate EoL care discussions cultivate patients' accurate prognostic awareness (PA),²⁰ allowing them to realistically appraise their illness/life expectancy and come to terms with their forthcoming death, thereby increasing the likelihood of issuing a DNR order.^{21,22} However, physicians worldwide tend to discuss DNR options late; they commonly present DNR options when curative anticancer treatments and nonpalliative measures fail^{23,24} (including failure of CPR to save a patient's life).^{1,15} Physician–patient DNR discussions may occur early in patients' terminal-disease trajectory only when patients request such a discussion,^{23,24} contrary to their

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expectation that physicians should initiate prognostic and EoL care discussions.²⁵ Healthcare professionals should develop effective interventions to cultivate patients' accurate PA early in their terminal-illness trajectory, enabling them to make informed EoL care decisions that avoid unnecessary suffering imposed by CPR that at best prolongs the dying process without meaningful survival.^{1,2}

Despite physician–patient prognostic and EoL care discussions being recognized as key to facilitating a DNR order before death by Enzinger et al²¹ and Mack et al,²⁰ respectively, few randomized clinical trials (RCTs) on the effectiveness of ACP interventions in facilitating accurate PA^{26–31} have had DNR orders as a primary or secondary outcome. Moreover, in a systematic review of the efficacy of 55 ACP interventions (1996–2013),³² facilitating completion of advance directives was an outcome in only 13 RCTs, with none for patients with advanced cancer for whom DNR orders are most relevant. A later 26-study systematic review on ACP purely for patients with cancer (2006–2016)³³ confirmed the previous review³² that DNR or code status documentation was an outcome in 3 studies, but the only RCT was by Epstein et al.³⁴ Furthermore, patient autonomy and self-determination in both EoL care and DNR orders have evolved late in Asian countries. However, no RCTs conducted in Asian countries have evaluated whether DNR orders are promoted for patients with advanced cancer.^{32,33}

Three RCTs by Epstein et al,³⁴ Stein et al,³⁵ and Patel et al³⁶ of patients with advanced cancer with a primary outcome of documenting DNR or advance directives have several design issues that can be strengthened. First, their research designs were not theory-driven, their aims did not focus on facilitating PA, and the approaches to ensuring treatment fidelity were not explicitly indicated. Second, 2 of the RCTs^{34,35} provided a single-session intervention long before the patient's death (mean, 310 days)³⁵ or measured DNR documentation only 1 month postintervention without follow-up until the patient's death.³⁴ In the other RCT,³⁶ only 55.6% to 57.1% of participants had died when the outcome was evaluated (15 months after enrollment). Finally, time proximity to death for the DNR order was examined in only 1 RCT.³⁵

We therefore analyzed 1 secondary outcome of a blinded RCT of our individualized, theory-based, interactive ACP intervention³⁷ in facilitating accurate PA among Taiwanese patients with advanced cancer in order to improve issuing a DNR order before death. We hypothesized that tailoring our intervention to participants' readiness for prognostic information and ACP to enhance physician–patient prognostic/EoL care discussions would increase participants' likelihood of accurate PA, allowing them sufficient time to consider their EoL

care goals and prepare, emotionally and practically, for EoL care decision-making to issue a DNR order earlier before patients in the control arm. Our ACP intervention was shown to decrease the psychologic symptoms of patients with advanced cancer, facilitate accurate PA 61 to 150 days before death, and reduce receipt of CPR in their last month, but it did not improve their quality of life, help them achieve their EoL care preferences, or reduce the receipt of intensive care unit care and mechanical ventilation in their last month.^{37,38}

Patients and Methods

Overview and Sample

Of 795 patients with advanced cancer consecutively referred by their primary oncologist and approached by our research assistants, 460 patient–family caregiver dyads (57.9%) were enrolled and randomly assigned 1:1 to the experimental and control arms from April 2013 through June 2017 and were observed through December 2017 (Figure 1 and supplemental eAppendix 1, available with this article at JNCCN.org). Allocation to the study arms was concealed by independently generating or assigning the random allocation sequence to a researcher not involved in patient recruitment, interventions, and assessments. Between-arm baseline characteristics, accurate PA, DNR order issued, and LST preferences were balanced at randomization.³⁷ Data collectors were blinded to arm assignment. No research staff were involved in clinical care. Detailed information has been reported previously about the study design, sample size calculation, participant recruitment, treatments for each arm, treatment fidelity assurance, and assessments.³⁷ The RCT study protocol (supplemental eAppendix 1) was approved by the ethics committee of the study site and registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01912846). All participants provided written informed consent before enrollment. Data analyses were conducted from July through August 2019.

Treatments

Participants in the experimental arm received a trans-theoretical model–based,³⁹ multifaceted, interactive ACP intervention including (1) repeatedly assessing readiness for participation in ACP or prognostic discussions; (2) providing interventions tailored to participants' readiness to engage in ACP or prognostic discussions to facilitate participants in the precontemplation, contemplation, or preparation stages moving to the action/maintenance stage³⁹; (3) promoting prognostic communication and EoL care discussions among patients, family caregivers, and physicians; and (4) providing educational aids (a workbook and a video) to enhance understanding of ACP and EoL care (supplemental eAppendix 1). Participants

in the experimental arm also received the same treatment as participants in the control arm: a sham treatment (with a format similar to that of the intervention) of (1) symptom-management education and (2) a booklet and video related to symptom management (supplemental eAppendix 1).

The intervention was tailored to participants' readiness for prognostic information based on the trans-theoretical model.³⁹ When we identified participants who had not thought about or did not want to know their prognosis (at the precontemplation stage), we explored their needs for prognostic information, thus raising their consciousness about the importance of prognostic information to motivate them to seek PA. For those who did not know but wanted to know their prognosis (at the contemplation stage), we encouraged them to discuss this desire with their physicians. For participants with inaccurate PA (at the preparation stage), our intervention was provided to verify and clarify any prognostic misunderstandings to promote accurate PA. For participants with accurate PA, we continually supported and reassured them that their EoL care goals and plan would be periodically reviewed based on changes in their health status and preferences.

Outcome Measures

Data on whether a DNR order was issued from enrollment until death and the date of the DNR order were retrieved from medical records and supplemented by caregivers' reports during bereavement follow-ups.

Patients' PA was assessed by asking if they knew their prognosis and if so, whether their disease was curable, might recur in the future but their life was not currently in danger, or could not be cured and they would probably die soon. Only patients who chose option 3 were recognized as accurately understanding their prognosis. Our measure of accurate PA—that is, “understanding that one's disease is incurable, life-threatening, or death is approaching”—maps onto the common conceptualization of PA.⁴⁰ Accurate PA was measured when it was first reported by participants in reference to time proximity to death (the period between death and assessment; ie, 1–30, 31–90, 91–180, and >180 days before death).

Time-Varying and Time-Invariant Covariates

For this longitudinal study, we adjusted for time-varying covariates (supplemental eTable 1) shown to influence issuing DNR orders⁴¹ (symptom distress, functional dependence, anxiety and depressive symptoms, and treatment dose [number of treatments provided]) and time-invariant covariates (sex, age, marital status, and educational attainment). Our time-varying covariates reflected our longitudinal data—that is, each participant had subject-specific responses at different data-collection

times before issuing the DNR order, and these responses likely differed between arms.^{42,43}

Data Collection

Participants' characteristics were assessed at enrollment before random assignment. Data on the outcome measure and time-varying covariates were collected by trained, experienced oncology nurses approximately every 3 to 4 weeks until participants declined participation or died (supplemental eAppendix 1).

Statistical Analysis

Effectiveness of our ACP intervention in facilitating DNR-order issuance before death was determined by intention-to-treat analysis.⁴⁴ We first used a chi-square test to examine between-arm difference in the proportions of participants with a DNR order issued before death, then we evaluated whether our ACP intervention promoted a DNR order before death by facilitating accurate PA, while controlling for treatment dose by multivariate logistic regression using hierarchical linear modeling (HLM)⁴⁵ with HLM 7 (Scientific Software International, Inc.). Finally, we examined whether our ACP intervention promoted a DNR order before death by facilitating accurate PA earlier in participants' terminal-illness trajectory using multivariate logistic regression with HLM for its main effect and considering interactions with accurate PA when it was first reported relative to death based on our hypothesis. We also controlled for treatment dose and for time-invariant and lagged time-varying covariates (physical symptom distress, functional dependence, anxiety symptoms, and depressive symptoms in the wave of assessment before the DNR order) to ensure a clear time sequence of effects on the outcome. The regression parameter for each independent variable was exponentiated to transform into an adjusted odds ratio (aOR) with a 95% confidence interval. Between-arm differences in the distributions of time proximity to death since issuing the DNR order were examined using chi-square and Wilcoxon–Mann–Whitney *U* tests because the time proximity to death since issuing the DNR order was not normally distributed.

Results

Patient Characteristics

Baseline sociodemographics, disease characteristics, and accurate PA were well-balanced between the experimental and control arms (Table 1) for the final 196 participants per arm who died and had supplied information on a DNR order (Figure 1). After enrollment, participants in the experimental and control arms received on average 5.56 ACP intervention sessions (SD, 6.22) and 4.76 (SD, 6.17) sham-treatment sessions and

Table 1. Participant Characteristics (N=392)

Variable	Experimental Arm n (%)	Control Arm n (%)	P Value
Patients, N	196	196	
Age, y			.057
≤45	36 (18.3)	18 (9.2)	
46–55	52 (26.5)	53 (27.0)	
56–65	62 (31.6)	76 (38.8)	
≥66	46 (23.5)	49 (25.0)	
Sex			.292
Male	139 (70.9)	133 (67.9)	
Female	57 (20.1)	63 (32.1)	
Marital status			.436
Married	163 (83.6)	166 (84.7)	
Not married	32 (16.4)	30 (15.3)	
Educational level			.554
≤ High school	164 (83.7)	164 (83.7)	
> High school	32 (16.3)	32 (16.3)	
Financial status			.707
Sufficient	176 (90.3)	175 (89.7)	
Insufficient	19 (19.7)	20 (20.3)	
Cancer diagnosis			.956
Liver-pancreatic	39 (19.9)	48 (24.5)	
Gastrointestinal	41 (20.9)	47 (24.0)	
Esophageal	31 (15.8)	30 (15.3)	
Pancreatic	33 (16.8)	27 (13.8)	
Lung	12 (6.1)	12 (6.1)	
Other (including hematologic malignancies)	40 (20.4)	32 (16.3)	
Metastasis			.320
Yes	185 (94.4)	188 (95.9)	
No	11 (5.6)	8 (4.1)	
Comorbidities			.196
Yes	126 (64.3)	135 (68.9)	
No	70 (35.7)	61 (31.1)	
Time since diagnosis			
Mean, mo (SD)	11.91 (15.85)	10.57 (13.85)	.374
SDS score, mean (SD)	34.72 (9.35)	35.94 (10.17)	.217
ESDS score, mean (SD)	35.10 (8.79)	35.10 (9.19)	.997
HADS-D score, mean (SD)	15.37 (4.34)	15.70 (4.47)	.264
HADS-A score, mean (SD)	7.72 (4.00)	8.21 (4.13)	.234
MQOL, mean (SD)	79.12 (21.65)	78.06 (22.58)	.634
Accurate prognostic awareness			.054
Yes	118 (60.2)	99 (50.5)	
No	78 (39.8)	97 (49.5)	

(continued)

Table 1. Participant Characteristics (N=392) (cont.)

Variable	Experimental Arm n (%)	Control Arm n (%)	P Value
Survival after enrollment, d			.178
Mean (SD)	141.91 (152.75)	121.69 (143.56)	
Median (range)	75.0 (5–675)	78.5 (1–802)	
Number of assessments after enrollment			.521
Mean (SD)	5.01 (4.70)	4.85 (5.05)	
Median (range)	3.0 (1–25)	3.0 (1–31)	
Number of treatments from enrollment to death			.198
Mean (SD)	5.56 (6.22)	4.76 (6.17)	
Median (range)	3.0 (0–33)	2.0 (0–40)	

Abbreviations: ESDS, Enforced Social Dependency Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; MQOL, McGill Quality of Life scale; SDS, Symptom Distress Scale.

were assessed 5.01 (SD, 4.70) and 4.85 (SD, 5.05) times, respectively. The last assessment was on average 22.96 (SD, 23.49) to 25.69 (SD, 49.71) days before death.

Intervention Effectiveness in Facilitating a DNR Order Before Death

At enrollment, only 9 (4.6%) and 8 (4.1%) participants in each arm had issued a DNR order (chi-square, 0.061; $df=1$; $P=.500$). After enrollment, 168 (85.7%) and 164 (83.7%) participants in the experimental and control arms, respectively, issued a DNR order before death (chi-square, 0.315; $df=1$; $P=.575$). However, participants in the experimental arm with accurate PA (87.7%) were more likely than participants in the control arm without accurate PA (77.0%) to have issued a DNR order before death (aOR, 2.264; 95% CI, 1.036–4.951; $P=.041$; Table 2). Specifically, after adjusting for covariates, participants in the experimental arm who first reported accurate PA 31 to 90 days before death (98.5%) were significantly more likely than their counterparts in the control arm (73.3%) to have issued a DNR order in the next wave of assessment (aOR, 13.365; 95% CI, 1.989–89.786; $P=.008$; Table 3).

When participants issued a DNR order before death, it was issued on average 9.74 (SD, 13.90; median, 5.0) and 15.18 (SD, 20.81; median, 6.0) days before death for the experimental and control arms, respectively ($P=.056$; Table 4). A DNR order was issued on the day of death by 20.7% to 26.2% of participants, with 35.9% to 38.1% and 52.4% to 61.3% issuing a DNR order within 3 and 7 days of death, respectively (Table 4).

Discussion

Our ACP intervention did not strongly facilitate the overall presence of a DNR order. However, participants

Figure 1. CONSORT diagram.
Abbreviation: DNR, do not resuscitate.

in the experimental arm with accurate PA were significantly more likely than those in the control arm without accurate PA to issue a DNR order in the next wave of assessment, especially if they first reported accurate PA 31 to 90 days before death. Nonetheless, participants in both arms generally issued DNR orders <15 days before death.

At enrollment in our study, few participants in both arms (4.1%–4.6%) had a DNR order on average 4 to 5 months before death. These figures were better than (2.6%),⁸ similar to (5.5%),⁹ or worse than (12.7%)¹⁷ those reported for patients with cancer and elderly patients

who were hospitalized, and worse than (20.3%) those reported for outpatients with cancer.²⁸ Nonetheless, evidence indicates that DNR orders are underutilized, given the futility of CPR for patients with advanced cancer.^{1,2} However, 83.7% to 85.7% of our participants issued a DNR order before death, close to the worldwide predeath prevalence of DNR orders for patients with cancer: 86% reported in the United States,⁹ 92% in Canada,¹⁰ 76% in Korea,⁴⁶ 74.7%¹¹ to 80.0%¹² in China, and 94.9% in Taiwan.¹³ Discrepancies between DNR orders issued at hospital admission,^{8,9,17} for outpatients,²⁸ or at enrollment in our study and at death^{9–13,18,46} may

Table 2. Intervention Effectiveness in Facilitating a DNR Order Before Death Among Participants With or Without Accurate Prognostic Awareness (N=392)

	%	aOR (95% CI)	P Value
Treatment dose		0.982 (0.941–1.026)	.422
Experimental arm with accurate PA	87.7	2.264 (1.036–4.951)	.041
Control arm with accurate PA	86.7	2.050 (0.929–4.524)	.075
Experimental arm without PA	78.0	1.076 (0.416–2.787)	.880
Control arm without accurate PA	77.0	Ref	

All participants' treatment doses (number of treatments provided) were controlled to ensure that our intervention effect was consistent across arms. Abbreviations: aOR, adjusted odds ratio; DNR, do not resuscitate; PA, prognostic awareness.

reflect lost opportunities to identify a DNR preference due to physicians' insufficiencies in addressing patients' CPR preferences and inadequate patient engagement, as reported by El-Jawahri et al,⁸ highlighting the need for effective interventions to identify the CPR preferences of patients with cancer and to facilitate issuance of DNR orders.

Although our ACP intervention did not strongly facilitate the overall prevalence of issuing a DNR order before death, as reported,^{34,35} it effectively promoted DNR order issuance by helping patients with advanced cancer to develop accurate PA (Table 2), especially among those first reporting accurate PA 31 to 90 days before death (Table 3). Higher rates were documented for advance directives in a lay health worker-led program³⁶ similar to our ACP, except that we explicitly assessed participants' readiness for prognostic information and engagement in ACP. The novel finding of our study is the significant role played by our ACP intervention in helping participants in the experimental arm achieve accurate PA in order to improve DNR order rates before patient death, as concluded in an observational study.²¹ Most important, our findings confirm that developing accurate PA at least 31 to 90 days before death allows patients sufficient time not only to realistically appraise their prognosis and come to terms with their forthcoming death but also to consider their EoL care goals and prepare emotionally and practically for EoL care decision-making, thereby increasing the likelihood of issuing a DNR order.²¹ We speculate that 31 to 90 days before death, when the participants in the experimental arm first developed accurate PA, may not be too far from death to dilute the urgent need⁴⁷ or too close to overwhelm patients to make an appropriate EoL care decision (ie, a DNR order). However, why and how 31 to 90 days before death was the most critical period for accurate

Table 3. Multivariate Analyses of Intervention Effectiveness in Facilitating DNR Order Before Death (N=392)

Variable	aOR (95% CI)	P Value
Intercept	19.163 (2.008–182.904)	.010
Arm		
Experimental	0.729 (0.255–2.084)	.556
Control	Ref	
Accurate prognostic awareness relative to time proximity to death, d		
Never	Ref	
≤30	2.208 (0.442–11.033)	.335
31–90	0.419 (0.155–1.130)	.086
91–180	1.725 (0.426–6.984)	.445
>180	0.841 (0.185–3.829)	.823
Arm by accurate prognostic awareness relative to time proximity to death, d		
Control*never	Ref	
Experimental*never	Ref	
Control*≤30	Ref	
Experimental*≤30	0.469 (0.063–3.472)	.459
Control*31–90	Ref	
Experimental*31–90	13.365 (1.989–89.786)	.008
Control*91–180	Ref	
Experimental*91–180	1.425 (0.185–10.948)	.734
Control*>180	Ref	
Experimental*>180	1.424 (0.243–8.352)	.695
Symptom distress	0.962 (0.918–1.009)	.114
Functional dependence	1.007 (0.962–1.054)	.773
Depressive symptoms	0.998 (0.890–1.119)	.968
Anxiety symptoms	1.142 (1.041–1.254)	.005
Sex		
Male	0.663 (0.337–1.306)	.235
Female	Ref	
Age	0.984 (0.957–1.012)	.254
Marital status		
Married	1.479 (0.682–3.206)	.322
Unmarried	Ref	
Educational attainment		
≤ Junior high school	Ref	
> Junior high school	1.199 (0.526–2.735)	.666
Intervention dose	0.971 (0.919–1.025)	.286

Abbreviations: aOR, adjusted odds ratio; DNR, do not resuscitate.

PA to influence the issuance of a DNR order warrants further in-depth exploration, preferably by qualitative studies involving patients and their family caregivers.

Our ACP intervention did not facilitate issuing an earlier DNR order, consistent with a report of an intention-to-treat analysis of an intervention comprising

Table 4. Differences in Time Proximity to Death Since DNR Order Issued (N=332)

	Experimental Arm (n=168)	Control Arm (n=164)	z/Chi-Square	P Value
Average	9.74 (13.90)	15.18 (20.81)	-1.910	.056
Median	5.0	6.0		
Range	1-109	1-104		
Days before death, n (%)			5.557	.235
1	44 (26.2)	34 (20.7)		
2-3	20 (11.9)	25 (15.2)		
4-7	39 (23.2)	27 (16.5)		
8-14	25 (14.9)	26 (15.9)		
15-28	27 (16.1)	25 (15.2)		
>29	13 (7.7)	27 (16.5)		

Abbreviation: DNR, do not resuscitate.

a pamphlet and patient-psychologist discussion about EoL care preferences.³⁵ However, Stein et al³⁵ reported that DNR orders were issued 2.2 times earlier for the intervention group than for the control group (median, 27 vs 12.5 days, respectively; $P=.03$) by per-protocol analysis for 47.3% to 64.6% of their originally randomized participants. Our participants' DNR orders were issued closer to death for both arms (median, 5-6 days before death) than those reported in Stein et al.³⁵ All participants in that study were aware of their prognosis, which may have facilitated earlier DNR orders. The median time proximities to death since our participants issued a DNR were longer than those reported in the United States (1 day)⁹ and China (1 day)^{11,12} but comparable to those reported in Canada (6 days)¹⁰ and Taiwan (7 days).¹³ Correspondingly, 20.7% to 26.2% and 35.9% to 38.1% of our participants ordered a DNR on the day of death and within 3 days of death, respectively, comparable to or better than reported prevalences: <26% in Canada,¹⁰ 28.1% in Korea,¹⁴ and 41.1% in China¹² on the day of death and 64.7% in Korea¹⁴ and 81.9% in China¹² within 3 days of death. Our findings and those in the literature regarding the time proximity between issuing a DNR order and death signal that physician-patient EoL care communication is delayed and suboptimal. Such late DNR orders probably reflect a lack of response to either curative anticancer treatments or LSTs^{8,17} and rushed decision-making as patients' physical condition deteriorates, as symptoms are exacerbated, or during medical crises^{1,8,15} despite vast clinical^{16,48} and research³³ efforts over the past 4 decades to improve CPR decision-making at EoL.

Strengths of this study include its interactive intervention tailored to participants' readiness for ACP, its rigorous blinded design to ensure internal validity, and

longitudinal examinations of accurate PA and time-varying covariates to appropriately disentangle the role of those factors in issuing a DNR order before participants' death. However, the generalizability of our findings to national and international target populations may have been compromised by sampling patients with a family caregiver from a single Taiwanese hospital. Our findings need to be replicated for patients with advanced cancer in countries where cultural, societal, and healthcare characteristics may substantially differ. Our repeated assessments (testing)⁴⁹ of participants' CPR/DNR preferences regarding their dying process may have sensitized and motivated participants in the control arm to prepare for EoL care, thereby threatening our study's internal validity and neutralizing/minimizing the intervention's effectiveness in facilitating DNR orders earlier in their terminal-illness trajectory. Furthermore, we focused on patient participants and did not consider family caregivers,^{22,41,50} despite the well-recognized power of Asian families in EoL care decisions⁵¹; physicians' attitudes, knowledge, and skills in facilitating patients' DNR decision-making^{23,41,52}; and institutional culture and policies about DNR orders.^{41,53} Studies should continue to evaluate how interventions can promote issuing DNR orders earlier in the terminal-illness trajectory considering the interactions of patients and their family caregivers' values and preferences with physician practice styles within specific hospital cultures and policies.

Conclusions

Our ACP intervention did not facilitate the overall presence of a DNR order. However, it did facilitate the issuance of DNR orders before death for patients with advanced cancer who had accurate PA, especially among those who reported accurate PA 31 to 90 days before death, but did not facilitate the issuance of DNR orders before death earlier than their counterparts in the control arm. Effective interventions are needed to overcome the challenges of finding an optimal time, from the patient, family, physician, and institute perspectives, to discuss prognosis and EoL care issues to facilitate the issuance of DNR orders earlier in the terminal-illness trajectory, thus avoiding potentially inappropriate CPR.

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Evaluating if an Advance Care Planning Intervention Promotes Do-Not-Resuscitate Orders by Facilitating Accurate Prognostic Awareness

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eTable 1: Measurement of Time-Varying Covariates

eAppendix 1: Study Protocol

eTable 1. Measurement of Time-Varying Covariates

Instrument	Characteristics	Scoring
Symptom Distress Scale (SDS) ¹	A 13-item, self-report scale with 11 symptoms, asking patients to rate the degree, frequency, and intensity of symptom distress, including nausea, appetite, insomnia, pain, fatigue, bowel patterns, concentration, appearance, breathing, outlook, and cough	Each item is rated on a 5-point Likert scale (1 = no distress; 5 = extreme distress) Total scores range from 13 to 65, with higher scores indicating greater distress
Enforced Social Dependency Scale (ESDS) ²	A 10-item, self-report scale, asking patients to rate their dependence on external sources to perform duties that are ordinarily taken for granted, such as eating, walking, and bathing	Each item is rated on a Likert scale from 3 to 6 points Total scores range from 10 to 51, with higher scores reflecting greater dependence on assistance for personal and social functioning
Hospital Anxiety and Depression Scale (HADS) ³	A 14-item scale with two 7-item subscales (anxiety and depression) asking patients to rate items according to how they have felt during the previous week	Each item is rated from 0 to 3 Total subscale scores range from 0 to 21, with higher scores indicating more severe depression or anxiety

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eAppendix 1. Study Protocol

An Interactive Advance Care Planning Intervention to Facilitate a Good Death for Patients With Cancer

Brief Summary

The purpose of this 5-year intervention study is to design, implement, and evaluate the effectiveness of an intervention aimed at facilitating prognostic communication and end-of-life (EoL) care decision-making to increase congruence between patients' preferred and received EoL care, improve patients' and family caregivers' quality of life (QoL) and psychological well-being, reduce utilization of futile aggressive healthcare resources at EoL, and facilitate bereavement adjustment.

Detailed Description

A randomized controlled trial (RCT) of a tailored, multifaceted intervention will be conducted on a consecutively recruited sample of 231 dyads of terminally ill patients with cancer and their family caregivers. Intervention effectiveness will be evaluated by comparing outcomes between patient-caregiver dyads in the experimental arm and the same number of dyads in a symptom-management education control arm.

Primary Objectives

To examine the extent to which the proposed advance care planning (ACP) intervention will (1) increase congruence between preferred and received EoL care among terminally ill patients with cancer, (2) improve QoL and reduce patients' and caregivers' depressive and anxiety symptoms during the patient's dying process, and (3) enhance family caregivers' bereavement adjustment.

Secondary Objectives

To determine the effectiveness of the proposed ACP intervention in facilitating patients' prognostic awareness and EoL care discussions among patients, families, and physicians; increasing patient-caregiver agreement on EoL care preferences; and reducing aggressive EoL care treatments for terminally ill patients with cancer.

Sample Size Calculation

Sample size will be estimated based on observational evidence that EoL care discussions between terminally ill cancer patients and their physicians increases congruence between patients' preferred and received EoL care.¹ This evidence was used because no intervention to date has been shown to directly increase congruence between preferred and received EoL care among terminally ill patients with cancer. Patients who reported having EoL care discussions with their physicians were more likely than those who did not have such discussions to receive EoL care consistent with their preferences (odds ratio [OR], 2.04; $P < .0001$)¹ and received significantly fewer aggressive medical interventions near death, with lower rates of cardiopulmonary resuscitation (0.8% vs 6.7%; adjusted OR [aOR], 0.16; 95% CI, 0.03–0.80), mechanical ventilation support (1.6% vs 11.0%; aOR, 0.26; 95% CI, 0.08–0.83), and intensive care unit (ICU) care (4.1% vs 12.4%; aOR, 0.35; 95% CI, 0.14–0.90), respectively. A sample of 124 to 190 dyads per arm would achieve 85% power to detect a between-arm difference in patient-physician EoL care discussions by 2-sided tests with $P < .05$. To compensate for the 18.5% attrition rate found in our previous longitudinal study,² 147 to 231 dyads per arm are needed. The proposed sample will target 231 dyads per arm to ensure adequate power to detect the hypothesized effects of the proposed intervention.

Participant Recruitment

Terminally ill patients with cancer will be consecutively referred by their participating oncologists based on the following criteria: (1) diagnosed with a terminal-stage disease that continues to progress with distant metastases and judged by their oncologists as unresponsive to current curative cancer treatment, (2) cognitively competent, (3) able to communicate with data collectors, (4) age >20 years, and (5) having a designated family caregiver who agrees to participate.

Family caregivers will be recruited if they are (1) family members of patients with cancer with a terminally ill disease as defined by this proposed study, (2) identified by patients as the primary person caring for them without financial reimbursement for that care, (3) age >20 years, and (4) agree to participate and can communicate with data collectors. Patients and family caregivers will be excluded if they participate in other research to facilitate prognostic awareness, ACP, QoL, or psychological well-being.

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eAppendix 1. Study Protocol (cont.)

Detailed information about patients' eligibility criteria will be given to patients' oncologists who agree to participate in this study. They will be asked to identify and refer all dyads of patients and family caregivers without judging their emotional readiness to talk about their prognosis and EoL care preferences. Referred patient and caregiver eligibility will be evaluated by data collectors who will invite them to participate in the study. Because QoL, depressive symptoms, and anxiety symptoms for both patients and family caregivers are primary study outcomes, patient–caregiver dyads will be excluded if either the patient or caregiver cannot communicate with the data collectors or refuses to participate.

Approximately 8 to 10 new dyads of terminally ill patients with cancer and their family caregivers will be recruited each month. After developing a detailed study protocol, we will recruit the targeted 462 participant dyads (231 dyads in each treatment arm). We will enroll and randomly assign eligible patient–caregiver dyads 1:1 to the intervention or attention-control arm without stratification.

ACP Intervention

The goal of this theory-based, tailored, multifaceted, interactive ACP intervention is to facilitate discussions among terminally ill cancer patients, their family caregivers, and their primary physicians about the patient's EoL care preferences and to honor the patient's wishes. To that end, the ACP intervention will clarify each participant's understanding of the patient's prognosis and treatment options and her/his readiness to engage in ACP, help participants appropriately weigh the benefits and burdens of medical treatments at EoL, and clearly define and document the patient's preferences for their oncologist to use later to guide EoL care decision-making that honors the patient's preferences. The intervention constitutes dynamic and multiple interactions between patients, family caregivers, and primary physicians and a trained, master's-prepared ACP interventionist with experience in oncology nursing and palliative care. The ACP interventionist will use 2 decision aids (a booklet and a video) to enhance participants' understanding of the essential elements in ACP and aggressive EoL care.

The major components of the proposed ACP intervention will include (1) repeated assessments of participants' readiness to engage in ACP; (2) specific interventions tailored to participants' readiness to engage in ACP; (3) facilitating prognostic communication and EoL care discussions among patients, family caregivers, and physicians; and (4) use of a booklet and a video educational aid to facilitate understanding of ACP and life-sustaining treatments at EoL.

The trained ACP interventionist will begin each course of the ACP intervention by independently and separately assessing each patient's and family caregiver's readiness to engage in ACP. The ACP interventionist will assess participants' understanding of how the illness is likely to progress, EoL care preferences and goals, and readiness to engage in ACP. "Course" refers to each repetition of the 4 major intervention components. Each course will assess participants' readiness for ACP and EoL care preferences to determine whether they have changed over time and to adjust the intervention accordingly. The participant's stage of readiness to engage in ACP will be determined according to the Transtheoretical Model.³ For this study, we propose that in the first stage, *precontemplation*, the participant is unaware of the prognosis or has no desire to engage in ACP planning. In the second stage, *contemplation*, the participant understands the relevance of ACP to his/her life and begins to consider his/her values and future treatment preferences. In the third stage, *preparation*, the participant commits to engage in ACP soon, but is not yet ready to do so. In the fourth stage, *action*, the participant overtly engages in ACP (eg, discusses and clarifies his/her EoL-care preferences with family members and healthcare professionals). In the fifth stage, *maintenance*, the participant has made EoL care decisions and can periodically evaluate these decisions given changes in her/his life status.

The intervention protocol in this trial will not follow a script for discussing prespecified topics. Rather, the trained ACP interventionist will have the flexibility to provide participant-centered care tailored to the participant's specific needs at each stage of readiness to engage in ACP. For participants in the precontemplation stage, the goal of the individualized intervention will be to address participants' lack of readiness to engage in ACP and to motivate them to think of the relevance of ACP. For participants in the contemplation stage, the ACP interventionist will discuss life-sustaining treatments and palliative care that may be applicable to that patient, explain the benefits and burdens of each treatment, and encourage patients and caregivers to evaluate these benefits and burdens from their own perspective. For participants in the preparation stage, the ACP interventionist will help them to determine specific EoL care preferences and to communicate their preferences and concerns to primary physicians. For participants ready to act on ACP, the ACP interventionist will communicate patients' and family caregivers' EoL care preferences to their oncologist, thus facilitating EoL care discussions to achieve a consensus on EoL care goals and specific treatments that could be used or withheld. For participants who have made EoL care decisions, the ACP interventionist will continually support and

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eAppendix 1. Study Protocol (cont.)

reassure them that their goals and EoL care plan will be periodically reviewed based on changes in the patient's health status and preferences.

To enhance consensus in perceptions of the prognosis and EoL care goals/preferences among terminally ill patients with cancer, their family caregivers, and physicians, the ACP intervention protocol is designed to facilitate discussions about these topics throughout the dying process. Because patients' preferences and concerns fluctuate over the dying process, a basic tenet of this intervention is that ACP will be revisited periodically to ascertain any changes in participants' values regarding an acceptable QoL and desirable EoL care as the patient's death approaches. After the initial intervention course, the ACP interventionist will interact with participants at least every month until the patient dies. If the patient's health status declines, as assessed by the primary physician, or the patient experiences sentinel events (eg, initiating a new chemotherapy regimen, deciding to undergo major surgery, admission to an ICU, initiating mechanical ventilation or new hemodialysis, diagnosis with central nervous system metastases), the next intervention course will be scheduled immediately to readdress the participant's EoL care goals and preferences. The tailored intervention will be provided according to the patient's specific needs.

Symptom-Management Educational Control Arm

The symptom-management educational control arm is designed to compare the effects of the multifaceted, interactive ACP intervention to those of a symptom-management educational intervention to rule out the Hawthorne effect. The control arm protocol will include prognostic disclosure and EoL care discussions as needed according to current clinical practice. This study arm will be provided by trained, master's degree-prepared nurses with experience in oncology nursing and palliative care. In the initial session for this arm, the treatment provider will give terminally ill patients with cancer and family caregivers a booklet and a video with educational materials on how to manage common symptoms and a list of available resources, including patient support organizations, as well as support and financial assistance through the hospital's social work department. We hypothesize that using a booklet and video on symptom management alone will not impact the outcomes, but will parallelize education received by the control arm as much as possible with that of the experimental arm. This hypothesis is based on a systematic review that found using informative material alone did not promote use of ACP.⁴ The control arm treatment provider will visit and interact with control arm participants according to the same schedule as for the experimental arm (weekly during hospitalization or monthly at outpatient visits until patient death) to assess their symptom distress and general well-being. Necessary referrals to physicians or social workers will be made for further management.

Data Collection Procedures

Participants will be assessed prospectively until patient death, loss to follow-up, study withdrawal, or the patient can no longer be interviewed. Both patients and their family caregivers will be assessed every 3 weeks for QoL and other outcomes to cover the most rapid changes in patients' physical condition and the most demanding period of caregiving until the patient's death.⁵ After each patient's death, his/her chart will be reviewed, and his/her caregiver will be interviewed to confirm the type of medical care received at EoL. At 1, 3, 6, and 13 months after the patient's death, bereaved family caregivers will be interviewed; 13 months was chosen instead of 12 months to avoid contamination with effects based on anniversary grief reactions.⁶

Strategies to Ensure Research Fidelity

1. Training of the treatment providers. The proposed ACP intervention requires professionals skilled in the content, techniques, and delivery of the intervention. The interventionist will be trained using competency-based education based on her previous oncology and hospice care experiences. The training will include an overview of the study protocol and procedures, a review of the developed booklet and video, and instructions in motivational assessments. The interventionist will be coached by the principal investigator (PI), who will serve as a role model, to assess and motivate participants at different stages of readiness for engaging in ACP and cooperating with physicians to coordinate and facilitate EoL care discussions. Before formal interventions can proceed, the interventionist will need to successfully demonstrate predefined competencies and consistency in delivering the ACP intervention after training and receiving individual feedback from the PI. Thereafter the study team will meet biweekly to review the interventionist's notes on intervention sessions and to provide feedback on difficult participant-management issues.

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eAppendix 1. Study Protocol (cont.)

The control arm treatment provider will be trained by the PI to understand the purposes of this symptom-management educational treatment, how to assess common symptoms for terminally ill patients with cancer, and how to use the booklet and video to help terminally ill patients with cancer and their family caregivers manage the patient's symptom distress. During training, the treatment provider will receive individual feedback from the PI. Before the treatment provider can formally provide symptom-management educational treatment, he/she will need to successfully demonstrate competencies and consistency in delivering the treatment. Thereafter, the study team will meet periodically to review the treatment provider's notes on symptom-management educational treatment sessions and to provide feedback on difficult participant-management issues.

2. Interventions provided to experimental-arm participants will be compared every 3 months with those received by control arm participants. Randomly selected patient-caregiver dyads in each treatment arm will be interviewed by the PI to check the extent to which treatments provided to them are consistent with the protocol for each arm.

3. To avoid bias, separate data collectors will be hired and trained to independently collect data for the experimental and control arms. These research assistants (RAs) will be blinded to treatment condition and trained to screen participants, obtain consent, and administer the project instruments without offering information. Procedures will be implemented to ensure that data collection is standardized. RAs' reliability will be established by comparing data collected by the RAs with that recorded by the PI on 5 pilot cases. PI-RA agreement must be 95% before RAs can collect data for the main study. Failure to reach this agreement rate will require additional training until the reliability level is acceptable. To maintain 95% PI-RA agreement, the PI will check reliability intermittently throughout the study.

4. To ensure continuing patient safety as well as the validity and scientific merits of the trial, an independent Data and Safety Monitoring Board (DSMB) will be organized. The DSMB will constitute a biostatistician experienced in statistical methods for clinical trials, a nurse researcher experienced in conducting RCTs, and a physician-scientist experienced in cancer care.

The DSMB will monitor and address the following issues: (1) sufficient and appropriate enrollment of participants, including compliance with the eligibility criteria for each dyad of terminally ill patients with cancer and family caregivers enrolled in the trial; (2) appropriate implementation of randomization; (3) comparability of baseline data between treatment arms; (4) protocol compliance, including treatments delivered to each treatment arm and data collection schemes; and (5) adverse effects (AEs), quality assurance for data validation, and registry procedures for Clinical Trial registration at ClinicalTrials.gov.

Treatments delivered to participants assigned to the intervention and symptom-management education arms will be compared every 6 months by interviewing randomly selected patient-caregiver dyads in each treatment arm to check treatment components provided to them.

The study team will record AEs and submit them in writing to the DSMB monthly, with immediate reporting of serious AEs (SAEs) to the DSMB and an oncologist with expertise in cancer care. Site-reported AEs/SAEs to its Institutional Review Board (IRB) will be dictated by local requirements.

No data will be analyzed before the study ends. Access to interim results, including results according to study arm, will be limited to DSMB members and the statistician who prepares the reports. The DSMB will review study data every 6 months, and the DSMB summary recommendations will be directed to the PI. A summary of the review of reported AEs/SAEs will be sent to the local IRB to ensure that the participating center will be informed of any pertinent safety issues.

The biostatistician will be responsible for ensuring quality of data submitted to the registry against the predefined range of each independent and dependent variable, as well as for assessing the accuracy and completeness of registry data by comparing the submitted data to the original data.

Data Analysis and Interpretation

1. All data will be scored and entered into a computer spreadsheet by an administrative assistant blinded to participants' arm allocation.

2. To test for baseline equivalence among participants in each arm, between-arm differences in baseline characteristics and identified outcomes will be assessed with 2-sided Fisher exact tests and chi-square tests for categorical variables and independent-sample Student's *t* tests for continuous variables.

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eAppendix 1. Study Protocol (cont.)

3. Intervention effectiveness will be examined using intention-to-treat regression analyses with generalized estimating equations (GEE). In the intention-to-treat regression analyses, all patient participants will be analyzed in the treatment arm to which they are initially allocated until they die, regardless of whether they complete or withdraw from the treatment.

4. Congruence between the preferred and received EoL care among terminally ill patients with cancer will be determined by comparing agreement between EoL care preferences elicited at the last assessment and EoL care received by the patient. Congruence will be expressed by the percentage of overall agreement and kappa coefficients to correct for the extent of agreement expected to occur by chance alone.

5. The impact of the intervention on congruence between the preferred and received EoL care among terminally ill patients with cancer, and on secondary outcomes (prognostic awareness, EoL care discussions, patient–caregiver agreement on EoL care preferences, use of futile aggressive EoL care, hospice use, and early hospice referral) will be determined by multivariate logistic regression using GEEs, while adjusting for confounding factors. We will also use the GEE model to examine the moderation effects of prognostic awareness, EoL care discussions, and patient–caregiver agreement on EoL care preferences on between-arm differences in congruence between the preferred and received EoL care among terminally ill patients with cancer, use of futile aggressive EoL care, hospice use, and early hospice referral.

6. Intervention effects on patients' and family caregivers' QoL and psychological well-being (anxiety and depression), as well as family bereavement outcomes (including QoL, depression, and grief reactions) will be examined by multivariate multiple regression using the GEE with simultaneous adjustment for confounding factors. We will also use the GEE model to examine the moderation effects of prognostic awareness, EoL care discussions, and patient–caregiver agreement regarding EoL care preferences on between-arm differences in patients' and family caregivers' QoL and psychological well-being before the patient's death, as well as family bereavement outcomes. The GEE model will also be used to examine how the intervention's effectiveness on patients' and family caregivers' QoL and psychological well-being before the patient's death and family bereavement outcomes will be moderated by aggressive EoL care and congruence between the preferred and received EoL care among terminally ill patients with cancer.

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