

Original Article

Simultaneous Care: A Model Approach to the Perceived Conflict Between Investigational Therapy and Palliative Care

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Abstract

Clinical trials of investigational therapy in patients with advanced cancer may not pay sufficient attention to quality of life (QOL) and supportive care issues, resulting in an adverse impact on the quality of care (QOC). We hypothesized that the simultaneous delivery of investigational therapy and a structured program of supportive care would result in measurable improvements in predefined outcomes without adverse events for patients, caregivers, or the physician/patient interaction. This report describes the findings of a trial designed to test the feasibility and initial results of such an approach. Forty-four patients accrued to Phase I or Phase II investigational therapy trials were simultaneously enrolled into a defined home care program focused on supportive care needs of the patient and family, as well as assessment of the toxicities of investigational therapy. These 44 patients constitute the Simultaneous Care (SC) cohort. Twenty patients receiving investigational therapy and the standard supportive care measures available through the Cancer Center served as a control group, designated the Usual Care (UC) cohort. We measured QOL using baseline and monthly assessments of the Functional Assessment of Cancer Therapy (FACT-G) instrument. This instrument measures four domains of well-being: physical, emotional, functional, and social/family. We prospectively defined QOC as: the percentage of hospice referrals; hospice length of stay; and number of cycles of chemotherapy administered. A summary score for the four FACT domains at each time point for each patient was calculated (FACT 4). The FACT 4 scores of the SC group improved compared to the UC group but did not reach a significant difference. Individual scores reflected a wide range of psychometric variability. A statistically significant difference in referral to hospice was seen in the SC group (35/44) compared to the UC group (8/15) ($P = 0.034$). The median length of stay in hospice was the same for both cohorts but the mean stay was greater in the SC cohort (54 days) compared to the UC cohort (37 days).

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The mean number of chemotherapy cycles was not different between SC and UC ($P = 0.25$). The self-reported acceptance by patients, caregivers, physicians and Cancer Center support staff was qualitatively excellent. Patients with advanced cancer at the time of enrollment onto investigational therapy should have made an explicit transition to palliative care goals but often have not. In the current health care environment, patients with advanced cancer without curative potential may be forced by their health provider or health insurer to choose between disease-directed therapy (including investigational therapy) or structured best supportive care programs. In this emerging era of targeted therapies, SC provides an approach designed to optimize palliative care goals while supporting the clinical research mission of offering patients with advanced cancer new and potentially better therapeutic interventions. SC is a system of care that enhances patient choice by allowing patients and families to have concurrent access to two beneficial options. SC may enhance coordination of care and facilitate patients' explicit transition from curative intent to palliative intent. In order to validate this approach, a randomized comparative trial evaluating SC has been initiated. J Pain Symptom Manage 2004;28:548-556. © 2004 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Simultaneous care, investigational therapy, ethics

Introduction

Patients with advanced cancer have at least two interventions available after they exhaust conventional therapeutic options. One is continued disease-directed therapy, ideally as a participant in a Phase I or Phase II investigational therapy protocol. The other intervention is best supportive care, also referred to as palliative care (PC). Referral to a hospice program is one common approach to palliative care, though other less structured approaches are often also available.

Several barriers complicate the choices that the physician and the patient face. First, patient/family dynamics can be a barrier. Patients with advanced disease at initial presentation may progress to death so rapidly that even the most effective family unit will be challenged to cope well. In addition, a number of patients and families have inadequate coping skills that impair good medical and personal decision-making.

Second, there is a regulatory barrier that discourages referral to hospice during investigational therapy. The criteria for entry into investigational therapy protocols and hospice are similar, except that normal organ function is usually required for investigational therapy. Both require that patients should have failed conventional therapy and have a limited life

expectancy. However, hospice programs are required to pay for all diagnostic studies and treatment, including investigational therapy, related to the terminal diagnosis. This is a financial obligation that most hospices cannot meet within the current per diem reimbursement.

A third barrier is a common perception by all parties involved, including physicians, patients, and hospice programs, that investigational therapy and palliative care cannot be administered simultaneously. When enrolled in investigational therapy, the physician and patient focus on goals related to the therapeutic intent of the protocol, sometimes to the exclusion or minimization of end-of-life issues and palliative care. An additional confounding factor bears consideration. Phase I and Phase II patients should have transitioned from curative goals, and protocols use explicit language defining the nature and extent of therapeutic response patients may reasonably expect. That said, patients and caregivers continue to think and act with curative intent and expectations of substantial disease remission or retardation.¹

Patients entered onto Phase I or early Phase II protocols epitomize this phenomenon of late referral or non-referral to hospice, with the attendant risk of failing to address palliative care issues focused on end-of-life. Confirming this impression, the Institute of Medicine recently issued a report that noted the poor state of

palliative care provided in the nation's cancer centers.²

Patients in early phase investigational therapy protocols have been described as vulnerable and unable to provide complete informed consent.³ The goals of Phase I and Phase II investigational therapy trials are to define toxicity and to assess response rate, respectively. The physician researcher expects response to Phase I therapy to be infrequent or transient whereas Phase II trials study known active agents with significant response rates but not curative results. Consent forms for Phase I trials are intended to provide information about risks and specific treatment-related toxicities, and explicitly state that the patient is unlikely to benefit from participation.⁴ A significant proportion of patients and some physician providers do not recognize or acknowledge the narrowly defined goals of these trials.^{1,5} On the other hand, health care providers involved with hospice or other palliative care programs may be unaware of the differences in design and intent of a first-in-human Phase I trial compared to a site-specific Phase II trial of a known active agent, and assume that all such studies provide little chance of therapeutic benefit.

When investigational therapy and palliative therapy are provided sequentially, patients and caregivers may have little or no opportunity to optimize the benefits of hospice or other structured supportive care interventions. Further, depriving caregivers of the opportunity to express anticipatory grief or participate in after-death bereavement services may increase the incidence of complicated grief and lead to less adaptive survivorship.⁶ Conversely, some cancer patients elect hospice programs when available therapies are known to result in improved survival, quality of life, and symptom control compared to supportive care alone.^{7,8}

Forcing patients to choose between the two options may eliminate patients who prefer palliative care but who would be willing to participate in clinical research. This unintentional exclusion may bias clinical trials accrual. In some cases this may cause patients to choose both diminished longevity and poorer quality of life.

There is no *a priori* reason to exclude palliative care during investigational therapy. We hypothesized that investigational therapy and palliative care can be provided simultaneously,

without toxicity, that is, without adverse patient, family, and provider reactions.

We report the results of an intervention that examines the quality of life and the quality of care of a cohort of patients entered onto investigational protocols who simultaneously were provided palliative care.

Methods

Patients

All patients entered onto a University of California Davis Phase I or Phase II cancer investigational therapy protocol were considered eligible for Simultaneous Care protocol entry. Randomized Phase III studies were allowed if they compared different chemotherapy regimens for advanced disease. Only one such study was considered, SWOG 9916, a comparison of mitozantrone and prednisone compared to estramustine and docetaxel for prostate cancer. Patients' treating oncologists asked eligible candidates to participate in Simultaneous Care.

Simultaneous Care patients signed a separate IRB-approved consent that permitted them to participate in the Simultaneous Care protocol. Those consented patients who lived within the service area of the University of California Davis Hospice Program (roughly 25-mile radius) received Simultaneous Care. Patients who lived outside the service area received usual care. The Usual Care or non-intervention group was used as a control cohort in this non-randomized pilot study. Potential selection bias differences in the two groups were recognized.

The Simultaneous Care Intervention

Simultaneous Care patients were assigned a nurse trained in both cancer chemotherapy and palliative care, and a social worker with inpatient, clinic, home health, and hospice patient care experience. As most services were provided in patients' homes, these employees were based in the UCD Home Care Services Department. They developed written plans of care as for any other patient in home health. The nurse visited the home two to three times a week or as needed and the social worker one to two times a week or as needed. They accompanied the patient and his/her family to most physician visits at the UC Davis Cancer Center. The nurse focused on chemotherapy toxicity, symptom

management of advanced cancer, and care coordination. The social worker focused on emotional support issues, family and interpersonal issues, and end-of-life planning.

Quality of Life Assessment and Statistical Analysis

The Functional Assessment of Cancer Therapy-General (FACT-G) was administered at study entry and at 4, 8, 12, and 16 weeks.⁹ The FACT-G measures four domains of well-being: physical, emotional, functional, and social/family. The study questionnaire was designed for self-administration, although it was at times completed via face-to-face or telephone interview. The method of completion depended upon patient convenience and satisfaction of the protocol requirement for administration at 30-day intervals \pm 2 days. The 30-day interval coincided most closely to cancer center visits for drug administration and was less burdensome to the patient than more frequent administration. Patients always used an unmarked copy of the questionnaire, whether administration was in person with research staff, by phone, or by return mail.

Responses from completed questionnaires were tabulated and cross-checked for accuracy utilizing two different research assistants who each compared entries with the completed questionnaires. For each patient, scores were calculated for the four FACT-G quality of life domains: emotional well-being, functional well-being, physical well-being, and social/family well-being.

Summary scores for the four FACT domains at each time for each patient were calculated. Univariate summaries were carried out to check for problems with floor and ceiling effects, skewness, or other potential problems for analyses assuming normality of data, using all data points from all times of observation. All four domains showed slight skewness toward the left (i.e., toward the low values of the scale) but the central 50% of the distribution was symmetric, with the mean and the median the same and the quartiles symmetric around the median, so no transformations were used.

A factor analysis was carried out to determine whether the four domains represented independent contributions or whether there was substantial correlation. Using the baseline data for all patients in both groups, 55% of the variation could be accounted for by a single dimension in the data, highly correlated with all four

subscales. The next most useful independent dimension accounted for 20% of the variation. The factor analysis results and the high correlation among the four domains supported creation of a single overall summary measure, which we called the FACT 4 (sum of the four scores at a given timepoint). The primary quality of life analyses were based on the FACT 4, and secondary analyses examined change in the four subscales separately.

Analyses of change in scores over time began with graphical and descriptive summaries, including plots of score over time for each individual, plots of mean scores, and univariate descriptive statistics (mean, standard deviation, and percentiles) for each time point. Repeated measures regression models with random effects¹⁰ were used to summarize the overall patterns of change and treatment differences. The model assumed that the average change in quality of life over the follow-up period was linear, with the same mean starting point but possibly different rates of change for the two treatment groups. Thus the model included coefficients for baseline score on quality of life, rate of change per month for all patients, and the difference between rate of change for Usual Care and rate of change for Simultaneous Care. The coefficient for difference in rates of change served as a test of the primary hypothesis. The model allowed for individuals to differ from the average path of quality of life both in their starting level and in their rate of change; these two person-specific random effects were assumed to follow a bivariate normal distribution. The observed value at a given timepoint for a given person was assumed to have additional, within-person random variation, independent of the between-person random differences, and normally distributed with a constant variance.

Quality of Care End Points and Statistical Analysis

Patients were tracked until death. The number of patients entered into a formal hospice program and each patient's length of stay in hospice were recorded. Referral to hospice was used as a quality of care outcome to evaluate indirectly the care team efforts to successfully refocus goals on palliative care after chemotherapy was completed.

The number of chemotherapy cycles administered was recorded and the two cohorts compared to test for intentional or unintended influence by the Simultaneous Care nurse or social worker on patient adherence/abandonment of investigational therapy.

Proportions using hospice were compared with Fisher's exact test and number of cycles of chemotherapy with Wilcoxon's rank-sum test, corrected for ties. All tests were two-sided at level 0.05.

Results

From March 31, 1999, to March 30, 2001, 64 patients were enrolled. During that time approximately 190 patients per year were enrolled at the University of California Davis Cancer Center in eligible investigational chemotherapy studies. There were occasional patients who chose not to participate. The primary limiting factor was the caseload ability of the Simultaneous Care nurse (no more than 12 at a time and each followed for 3–6 months). The nurse maintained a full caseload, which prevented the admission of otherwise qualified and willing patients.

The characteristics of the patients are shown in Table 1. Forty-four patients were entered into the intervention or Simultaneous Care arm and twenty patients were entered into the non-intervention or Usual Care arm. Of ten physicians eligible to enroll patients, ten entered patients into the Simultaneous Care protocol. The

two cohorts were similar in sex distribution ($P = 0.97$) and age ($P = 0.20$). The two cohorts did have significant cancer diagnosis differences. For example, a greater proportion of patients in the Usual Care group had GU tumors (11/20) than the Simultaneous Care group (6/44), whereas non-small-cell lung cancer was more frequent in the Simultaneous Care group (17/44) than the Usual Care group (3/20).

Adverse Events

No patient disenrolled from Simultaneous Care as a result of discussions of end-of-life issues, palliative care discussions, or conflict between investigational therapy and palliative care goals or providers. No physician declined to offer Simultaneous Care enrollment or encouraged disenrollment. The qualitative consensus, derived from physician questionnaires given to each physician for each patient, was that the Cancer Center personnel not only encouraged Simultaneous Care but also came to expect the nurse and social worker as routine support, potentially redefining *usual care*. Repeated requests from Cancer Center nursing staff to add patients also contributed to this impression.

Quality of Life Results

Univariate analysis of all FACT 4 scores included a range of 25–106 (maximum of 108), mean 68.1 (SD 16.0) and a median of 68 (quartiles 59 and 78).

The initial FACT 4 score for Simultaneous Care was 64.7 and for Usual Care was 68.3. Figure 1 depicts slopes of the average change over time for Simultaneous Care and Usual Care. The Simultaneous Care change was +0.61 and the Usual Care was -0.77 , a difference of 1.38 points per month in favor of Simultaneous Care (95% CI -0.78 to 3.54, $P = ns$).

There was substantial variability both between and within persons. Figure 2 shows graphs of nine individual patient scores, including five Simultaneous Care patients and four Usual Care patients. Each patient's FACT 4 score is depicted over time. The range of initial FACT 4 scores at the initiation of therapy is obvious. This range demonstrates the highly variable physical and emotional suffering that patients may report at any given point.

Table 1
Demographics of Patients Entered

	Simultaneous Care	Usual Care
Total (men/women)	44 (24/20)	20 (11/9)
Median age (range)	62 (26–79)	57 (36–80)
Diagnosis		
NSCLC	17	3
Prostate	4	5
Colorectal	5	1
Unknown primary	4	
GYN	3	
Upper GI	2	1
Breast	2	3
TCC	2	1
H&N	1	
Melanoma		1
Renal		5
Oncologists	8	7
Clinical research associates	6	2

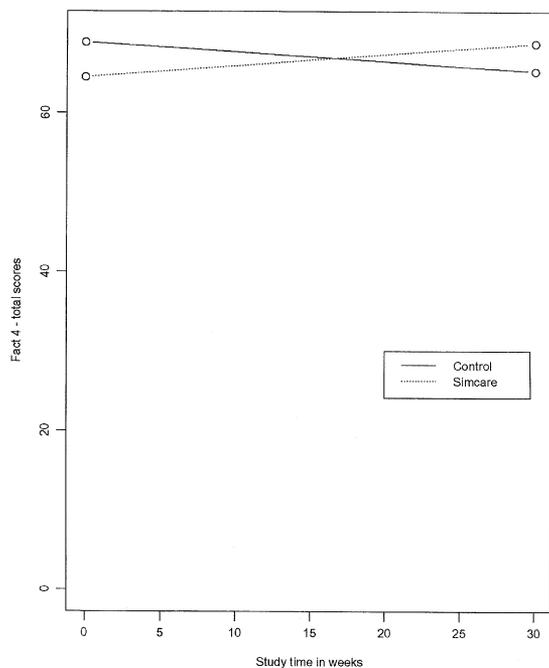


Fig. 1. Study time in weeks is shown on the x-axis; zero is entry into the simultaneous care study. The y-axis is the total of the four FACT G domain scores. The lines depict the estimated mean path followed over time by patients in simultaneous care and usual care.

The comparative changes over time in patients' scores are qualitatively different. For example, the slope in Figure 2, Patient 'a' shows a substantial increase in score while Patients 'd' and 'i' show remarkable, steady deterioration. Several show wide swings at different time points and emphasize that the oncology team needs to be prepared to offer different intensities of support at sequential visits.

Quality of Care Results

Table 2 shows ultimate outcomes and hospice utilization for both cohorts. As of December 1, 2002, 42 of the 44 Simultaneous Care patients have died. Thirty-five of the 44 died with hospice, 3/44 died on therapy, 4/44 died without hospice, and 2/44 are alive and off therapy without hospice.

Of the 20 Usual Care patients, 15 have died. Seven of the 15 without hospice after therapy was completed, 8/15 died in a hospice program, and 5 remain alive. The mean days in hospice was the same in both cohorts, but the median was higher in Simultaneous Care (54 days) compared to Usual Care (37 days).

Among those who died after completion of therapy, the proportion that entered hospice programs was greater in the Simultaneous Care than in Usual Care (92% vs. 53%, $P = 0.034$, Fisher's exact test).

Patients in Simultaneous Care received a mean of 3.8 cycles of chemotherapy (SD 2.1, range 1–8) and those in Usual Care received a mean of 4.5 cycles (SD 2.6, range 1–12). The means are not statistically different ($P = 0.25$, 95% CI -0.5 to 1.9 cycles).

Discussion

This study suggests that palliative care can be introduced simultaneously with investigational cancer therapy without adverse events. No conflicts between the Simultaneous Care team and the medical oncologists or primary providers were recorded. No patient withdrew from Simultaneous Care or refused to visit with the Simultaneous Care team. No physician or other provider within the Cancer Center reported an adverse event due to the intervention. That is, the introduction of palliative care along with disease-directed therapy neither undermined patient participation in clinical research nor adversely affected the patient/physician relationship.

A significantly higher proportion of Simultaneous Care patients elected hospice care. Future randomized studies with larger sample sizes will be necessary to confirm improvement or deterioration in quality of life, differences in utilization of hospice, and variation in survival.

These results use the FACT to demonstrate changes in quality of life over time. We are more closely analyzing the events surrounding the changes in FACT 4 for these patients. However, we would speculate that these scores could be correlated with coping abilities and that, at initiation of therapy, subgroups of patients with better or worse coping abilities can be identified. More robust instruments may also capture the underlying reasons for these differences.

The FACT 4 scores showed that there was a wide variation in the patients' initial scores. As importantly, although a number of patients showed quality of life deterioration over time on study, that rate was variable. A subgroup of patients might be identified who are able to maintain their quality of life and could be expected to need less support while others require

Table 2
Patient Outcome and Referral to Hospice

	Simultaneous Care	Usual Care
Total patients	44	20
Died on therapy	3	0
Died without hospice	4	7
Received hospice	35	8
Median days in hospice	54.5	37
Alive	2	5

The tailoring of the intensity of the intervention to the need of the patients, as measured by FACT-G was not done, as no immediate feedback was given to the care team based on the FACT scores. Reduced or increased savings to the health system needs to be measured prospectively. Only a true control group would be able to generate such a comparison.

Several new quality-of-life tools are available that may better capture the different domains of quality of life of both the patient and the caregiver. An after-death tool that captures the course, duration, and outcome of bereavement would also have been useful.

This study is limited by the modest sample size and the non-random assignment to treatment. In addition, the intervention was carried out at only one site, using physicians and staff experienced in palliative care.

Strengths of the study include its use of a standard measure of quality of life, longitudinal sampling, the comprehensive follow-up, the minimal drop-out from the study, and the use of objective secondary measures of toxicity and therapeutic outcome.

Simultaneous Care is a system of support that enhances patient choice. Patients are not asked to choose between two reasonable options, disease-directed therapy and palliative care. Rather they have an opportunity to receive both, each with a different set of goals, benefits, and burdens.

Simultaneous Care is a model of care that may enhance the coordination of care from the home to the clinic or cancer center. The Simultaneous Care team can explore issues not suited to thorough exploration during a clinic visit. The patient and family can prepare issues in advance that need to be raised at a clinic visit. Personnel with specialized training in psychosocial care and intervention can explore familial, existential, or interpersonal issues in the safe, comfortable setting of the home.

Simultaneous Care is an approach that addresses the ethical conflict posed by clinical trials.^{3,13,14} Whether illusory or actual, there is a dissonance between disease-directed therapy and palliative care. The dissonance is recognizable in emotions and attitudes such as frustration, anger, and expectations not consistent with stage of illness—for example, requests for resuscitation despite advanced disease, and the pursuit of alternative or unproven therapy.¹⁵ Systems of medical care and reimbursement may amplify this dissonance by obstructing effective transitions in the goals of patients and families as the disease progresses.

Perhaps the conflict grows out of the misapprehension that palliative care should be applied only in the face of advanced disease. In fact, progressive palliative care should be integrated into caring from diagnosis forward.¹⁶

The transitions from an emphasis on therapeutic goals of cure to control to palliation may evolve over years. Late in chronic or terminal illness, the shift from curative goals to predominantly palliative goals provokes strong reactions from many patients and caregivers. Often, the transitions are not explicitly stated or discussed. Thus when viewed as an either/or proposition, palliative care can look like giving up on therapy or giving up on the patient. Concurrent delivery of therapeutic and palliative care sustains hope and promotes a smoother transition from curative to supportive care goals.

Entry into an investigational protocol should be a sentinel event that prompts vigorous, explicit discussion of changing goals and the growing importance of palliative care. Reduced physical and emotional suffering combined with personal growth serve as the primary goals of palliative care. The explicit definition of goals redefines success and is the underpinning of the maintenance of hope.¹⁷

Simultaneous Care is a model that introduces end-of-life issues early enough for patients and families to benefit fully from specialized supportive care programs including hospice. Using this model, physicians and health systems that provide both disease directed therapy and palliative care are more fully addressing the comprehensive physical, medical, psychosocial, and spiritual needs known to accompany terminal illness.

This model of simultaneously providing relief of physical and emotional suffering and either

intensive disease directed therapy or clinical research therapeutics is broadly applicable to settings that emphasize investigation, developmental therapeutics, or that treat the severely ill patient. The model extends beyond oncology. Organ transplantation, new device testing, advanced non-cancer diagnoses like congestive heart failure or renal failure, and attempted resuscitation of critically injured or ill patients, including pediatric patients, are some of the venues potentially well-suited to the application of a Simultaneous Care model.

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