Palliative Care and Phase 1 Trials

Intervention to improve quality of life and provide education

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BACKGROUND: Patients in phase 1 clinical trials often have significant symptom burdens and quality-of-life concerns that increase as they progress along the cancer trajectory and experience drug toxicities from the clinical trial.

OBJECTIVES: The interdisciplinary intervention described is aimed at providing optimum palliative care to support patients with solid tumors participating in a phase 1 clinical trial.

METHODS: The intervention includes a baseline evaluation using quantitative surveys, a comprehensive palliative care assessment by a research nurse based on patient baseline evaluation, and a goals-of-care discussion by the treating oncologist. The second component includes an interdisciplinary meeting where palliative care recommendations are made, followed by two patient education sessions.

FINDINGS: The initial experience with the palliative care intervention suggests a need for support for this population, as well as potential benefits from integrating palliative care for patients enrolled in phase 1 clinical trials.

KEYWORDS
palliative care; phase 1 clinical trials; quality of life; symptom burden

DIGITAL OBJECT IDENTIFIER
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PHASE 1 CLINICAL TRIALS OFFER THE OPPORTUNITY TO ADVANCE SCIENCE in oncology and improve survival. This article describes the development of an intervention and a study in progress supporting the need for integration of palliative care for patients on clinical trials. In addition, the literature is reviewed to illustrate the palliative care needs of patients in phase 1 trials.

Patients enrolled in phase 1 clinical trials are generally less symptomatic and have higher function than patients with advanced disease. However, patients in phase 1 trials still have a significant symptom burden. A study by Hui et al. (2010) reported that patients in phase 1 trials had better performance scores (Eastern Cooperative Oncology Group, 0–4), but a symptom burden similar to other patients with cancer, with an average pain score of 5.3 on a 0–10 scale (with 10 indicating worst pain) and a fatigue score of 5.7 on a 0–10 scale (with 10 indicating worst fatigue). Ninety percent of patients in phase 1 trials experienced fatigue, but only 24% experienced vomiting (Parsons, Baracos, Dhillon, Hong, & Kurzrock, 2012). In a study by Finlay, Lu, Henderson, O’Dwyer, and Casarett (2009), patients in phase 1 trials had a symptom burden similar to non-enrolled patients, but after adjustments for performance status scores, the patients in phase 1 trials were more likely to have 5 of the 10 symptoms assessed with the Memorial Symptom Assessment Scale, with greater severity for 6 of 10 symptoms.

In addition to a baseline symptom burden, phase 1 trials are known to increase patient symptoms. As patients progress on the cancer trajectory, performance status worsens and symptoms increase. Clinical trial drugs may have toxicities that cause side effects and increase clinic visits, time away from family, and diagnostic testing. Targeted therapy may cause side effects in addition to existing disease and medication side effects (Cassel et al., 2016). These contribute to a decrease in quality of life (QOL).

Research has revealed that patients in phase 1 trials are highly motivated and willing to take treatment chances. In a report by Agrawal et al. (2006), 90% of patients in a phase 1 trial would risk taking an unproven drug with a 10% chance of mortality. In the same study, 84% of patients said they were aware of hospice and palliative care options, but only 6% had considered these options. However, more recent research reflects patients’ unwillingness to participate in clinical trials, with only 35% of Americans saying that...
they are likely to enroll in a trial. New data show that only 40% of Americans view clinical trials favorably, citing barriers to clinical trial enrollment such as side effects, safety, insurance coverage, inconvenience, “feeling like guinea pigs,” and general skepticism (Memorial Sloan Kettering Cancer Center [MSKCC], 2016). This negative public view is occurring at a time when the oncology community is calling for increased clinical trial participation.

**Literature Review**

Prior reviews have documented patients’ failure to understand treatment intent or phase 1 trial alternatives, realistic benefit and risk expectations, and the right to withdraw from or not enter a trial (Cox, Fallowfield, & Jenkins, 2006). Despite a patient’s terminal illness and average survival of just several months, oncologists rarely talk about prognosis during phase 1 trials (Jenkins, Anderson, & Fallowfield, 2010; Jenkins et al., 2011). A national poll of 600 respondents found that physicians see clinical trials as a treatment of last resort, even if they are available in early treatment phases (MSKCC, 2016). The poll suggests that providers consider clinical trials for patients across the cancer spectrum and communicate these opportunities. The authors concluded that “failing to consider clinical trials at every stage of cancer diagnosis and treatment can represent a significant missed opportunity, primarily for patients, as well as for doctors and researchers trying to develop better therapies” (MSKCC, 2016, para. 8).

Data have shown that education can increase patients’ willingness to enter clinical trials, with patients’ positive impression improving from 40%–60% when the trial was briefly explained (MSKCC, 2016). Fallowfield, Solis-Trapala, and Jenkins (2012) tested a provider intervention that appears to improve communication about phase 1 trials. Similarly, Kass et al. (2009) researched ways to increase patients’ understanding of phase 1 trial participation; however, data did not indicate a better understanding of treatment goals and options, as has been repeatedly observed with concurrent palliative care consultation (Smith et al., 2012; Temel et al., 2011).

In a study of more than 6,000 patients, African Americans were at least as likely as White patients to be referred for inpatient palliative care consultation, lived longer than White patients after consultation (25 versus 17 days), and had rates of hospice use that exceeded those of Whites (59% versus 51%) (Sharma et al., 2015). Palliative care consultation appeared to allow providers to bring up advance directives and do-not-resuscitate (DNR) status.

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**TABLE 1.**

**CONCEPTUAL FRAMEWORK FOR THE INTEGRATION OF PALLIATIVE CARE INTO PHASE 1 CLINICAL TRIALS**

<table>
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<th>NATIONAL CONSENSUS PROJECT GUIDELINES DOMAIN</th>
<th>APPLICATION OF GUIDELINES TO PHASE 1 CLINICAL TRIALS</th>
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<td>Palliative care assessment and intervention will be concurrently provided with phase 1 clinical trials.</td>
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<td>Physical aspects of care</td>
<td>Focus on symptom concerns common to advanced cancer and the type of investigational agent used for treatment.</td>
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<tr>
<td>Psychosocial and psychiatric aspects of care</td>
<td>Focus on psychosocial issues common in advanced cancer and address issues that are specific to patients participating in a phase 1 clinical trial.</td>
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<td>Social aspects of care</td>
<td>Address family distress, social support, and financial burden associated with advanced cancer and participation in phase 1 clinical trials.</td>
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<td>Spiritual, religious, and existential aspects of care</td>
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<td>Cultural aspects of care</td>
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*Note.* Based on information from National Consensus Project for Quality Palliative Care, 2013.

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“Despite a patient’s terminal illness, oncologists rarely talk about prognosis during phase 1 trials.”
example, among African American patients at one hospital (35% of whom had cancer), 65% agreed to DNR orders (Sacco, Carr, & Viola, 2013; Zaide et al., 2013). In addition, palliative care consultation with a specific emphasis on a goals-of-care discussion appeared to equalize the African American patients electing hospice with White patients; those who discussed code status had twice the rate of referral to hospice (odds ratio = 2.14) (Enguidanos, Vesper, & Goldstein, 2013).

No randomized, controlled trials exist regarding palliative care concurrent with phase 1 care. However, two trials show preliminary evidence of benefit. The first study was a quasi-randomized study with 44 patients enrolled in phase 1 or 2 trials, assigned to simultaneous care (a homecare program focused on supportive care needs) or usual care (Meyers et al., 2004). The patients in the simultaneous care group had access to a palliative care– and chemotherapy-trained nurse and a social worker with hospice experience, who together developed a written plan of care. The number of chemotherapy cycles did not differ between patients in the simultaneous care and usual care groups. More patients in simultaneous care (35 of 44) than in usual care (8 of 15) were referred to hospice (p = 0.034). The median length of hospice stay was the same for both cohorts, but the mean stay was greater in the simultaneous care cohort (34 days) compared to the usual care cohort (37 days). The investigators concluded that simultaneous care may enhance care coordination and facilitate patients’ explicit transition from curative to palliative intent.

In the second trial by Meyers et al. (2011), 476 patient and caregiver dyads were studied, with the patients undergoing phase 1, 2, or 3 cancer treatment at three cancer centers. The dyads were randomized to usual care or to usual care plus COPE (Creativity, Optimism, Planning, and Expert information), which was labeled as the Simultaneous Care Educational Intervention (SCEI) (Meyers et al., 2011). The primary endpoint of the trial was global QOL, with patients’ or caregivers’ problem-solving abilities as a secondary endpoint. No difference was noted in the rate of change of patient QOL between groups. Caregiver QOL scores declined, but at a lesser rate in the intervention group, which was statistically significant (p = 0.02). In planned secondary analyses, the caregivers in the SCEI group had significantly less decline in psychological, social, and spiritual QOL scores. Over time, the impact of COPE on the SCEI group increased and allowed care to remain stable.

Researchers continue to refine palliative care methods to provide quality of care throughout the disease trajectory. Dy et al. (2011) identified key aspects of end-of-life cancer care, targeting areas for quality improvement and measuring progress in an academic medical center. The authors emphasized the importance of integrating palliative care across the trajectory of cancer.

Hui et al. (2014) conducted a retrospective study of 366 adult outpatients who died of advanced cancer during a six-month period. Early palliative care referrals (more than three months before death) were associated with fewer emergency department visits (p < 0.001), hospitalizations (p < 0.001), hospital deaths

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**FIGURE 1.**
**SUGGESTED COMPONENTS FOR GOALS-OF-CARE DISCUSSION**

**ILLNESS UNDERSTANDING**
- Inquire about how people like to get medical information.
- "Are you the sort of person who wants to know all the details, or not? How about discussion of what might happen in the future?"
- Inquire about illness and prognostic understanding.
- "What do you want to know about your illness? What do you know about your situation?"
- Offer clarification of treatment goals, including phase 1 treatment.
- Always check with the treating oncologist first about realistic prognosis and future options.
- Patient perception, family perception, and reality
- Understanding after discussion of reality
- Address adapting to changed goals and likely death from cancer.
- Offer clarification of adaptation to changed goals and foreseeable death on several visits.

**SYMPTOM MANAGEMENT**
- Start with the symptoms first because these are considered to be safe and allow trust to be established.
- Always use a symptom assessment tool, such as Edmonton or Memorial Symptom Assessment scale.
- Inquire about uncontrolled symptoms with a focus on the following:
  - Pain
  - Pulmonary symptoms (cough, dyspnea)
  - Fatigue and sleep disturbance
  - Mood (depression, anxiety)
  - Gastrointestinal (anorexia, weight loss, nausea/vomiting, constipation)
  - Other symptoms expected from the phase 1 treatment
- Focus on symptom management as a part of the goals of care. Inquire about spirituality and religion. Ask, as routine, “Is religion or spirituality important to you?” and, unless there is active disinterest, “Would you like to see a chaplain?”

**DECISION MAKING**
- Inquire about decision making.
- Assist with treatment decision making, if necessary.
- Assess coping with life-threatening illness by patient and family.
- "This must be hard on you and your family. How are you coping?"

**OTHER COMPONENTS**
- Referrals and noting new prescriptions
- Identify a care plan for future appointments.
- Indicate referrals to other care providers, and communicate directly by fax, email, or electronic health record.
Palliative care is cited as providing better communication, symptom control, and treatment options, and improving QOL. The American Society of Clinical Oncology has updated recommendations that all seriously ill patients with cancer be given concurrent palliative and oncology care (Ferrell et al., 2017). Increasing evidence has shown that palliative care can lengthen patient survival, perhaps because palliative care goals include avoiding futile treatment and controlling symptoms, leading to improved survival with psychological and physical benefits of care.

Patients in phase 1 clinical trials may benefit from interdisciplinary palliative care that provides symptom relief, psychosocial support, and a better understanding of illness goals and treatment options, while concurrently receiving disease-directed therapies. With the rapid growth of palliative care, randomized trials have documented improved clinical outcomes (Cassel et al., 2016).

If palliative care enables patients to stay in clinical trials longer, with better management of treatment toxicities, decreased symptom burden, and improved QOL, palliative care may help advance cancer science. An article by Smith and Hillner (2011) documented the financial savings associated with palliative care.

**Conceptual Framework**

This National Cancer Institute–funded study is in year three of a five-year project and has accrued 287 patients to date. The study uses the *Clinical Practice Guidelines for Quality Palliative Care* from the National Consensus Project for Quality Palliative Care (2013) to guide study design and intervention content. The guidelines recognize that multidimensional patient support is essential in quality palliative care, and that support promotes the integration of palliative care as part of the cancer care continuum. The application of guideline domains to this study of palliative care integration (PCI) into phase 1 clinical trials is presented in Table 1.

The current randomized clinical trial tests a PCI administered concurrently to patients with solid tumors who are participating in a phase 1 clinical trial. The PCI is being conducted at two comprehensive cancer centers, City of Hope Medical Center in Duarte, California, and Johns Hopkins Cancer Center in Baltimore, Maryland. This multi-site, randomized PCI clinical trial evaluates key outcomes and, hopefully, will provide a model for other cancer settings where phase 1 trials are conducted. This innovative design brings together leading palliative care clinicians, researchers, and medical oncologists to test an interdisciplinary intervention that will provide optimum palliative care to support patients through clinical trials.

For the experimental PCI group, the study is initiated at the time of accrual to a phase 1 trial but prior to administration of the first phase 1 treatment dose. Participants are randomized to the trial. The intervention includes completion of baseline evaluation using quantitative surveys, comprehensive palliative care assessment by a research nurse based on baseline evaluation of the patient, and a goals-of-care discussion. Goals of care are discussed by the treating oncologist or the palliative care team if the oncologist defers, guided by a standard protocol (see Figure 1).

The PCI’s second component is initiated following the first dose of phase 1 treatment and completed within one month of the first treatment. This component includes an interdisciplinary team meeting, where palliative care recommendations are made. Two patient education sessions follow (see Figure 2), covering QOL-related domains of physical, social, psychological, and spiritual well-being. Based on interdisciplinary team recommendations, supportive care referrals to social work, nutrition, and psychology services are made. Patients in the usual care group receive the usual care, and each group is reevaluated at 4, 8, 12, 16, 20, and 24 weeks following treatment initiation. Because the 12-week time point is designated as the key outcome point, patients in the usual care group are offered the intervention after completing the 12-week data collection. In addition, a chart audit is conducted at the conclusion of the study to document variables, such as the patient’s...
ability to complete the trial, referrals to supportive care services, advanced directive completion, hospitalizations, and other aspects of resource use.

**Case Example**
The following case example is included to illustrate the experience of a patient receiving the PCI.

Elizabeth is a 49-year-old, married, female, native Californian, and the mother of one daughter and one son, ages 29 and 27, respectively. She and her spouse were self-employed at the time of her diagnosis. About six months prior, Elizabeth was suffering lower back pain and pelvic cramping, and lost 20 pounds during a three-month period. More recently, she had been experiencing severe abdominal pain, abdominal bloating, and anorexia. An ultrasound showed abdominal ascites. A paracentesis was performed and yielded 2.5 L of fluid. Cytology revealed adenocarcinoma considered to be an ovarian primary. Further diagnostics with a computed tomography scan found an adenexal mass with enlarged abdominal lymph nodes.

Elizabeth was evaluated at the cancer center in surgical gynecology and medical oncology, where a debulking surgery followed by chemotherapy was recommended, along with additional testing for tumor markers to ascertain the most appropriate treatment regimen. The surgery was completed, and the final pathology revealed a stage IIIIC high-grade serous adenocarcinoma. Her preoperative CA-125 was 1,289, which decreased to 21 postoperatively.

Upon recovery, Elizabeth was admitted to the hospital to receive a chemotherapy regimen of intraperitoneal cisplatin and paclitaxel for the planned six cycles. Eight months later, imaging revealed a recurrence in her abdomen and regional lymph nodes. She also suffered bilateral hydronephrosis, mandating stent placement. After stent placement, she began carboplatin and doxil and completed four cycles of the planned six cycles. Nausea, vomiting, and the need for bilateral stent replacements necessitated hospital readmission. Further workup showed disease progression.

Because of the disease’s progressive nature and available treatment, she consented to a phase 1 clinical trial of P53MVA vaccine in combination with gemcitabine. The oncologist discussed the goals of care with Elizabeth and her spouse, and they agreed to participate in the palliative care study. Two teaching sessions in four QOL domains were conducted. After the sessions, the APRN advised the physician that Elizabeth did not have an advance directive, and Elizabeth was consulted about this need. She tearfully agreed to implement an advance directive, given her disease state. The clinical social worker assisted, and the advance directive was notarized and placed in the electronic health record.

The APRN also referred Elizabeth to the pain and palliative care team for an evaluation of her increasing abdominal and back pain. She was placed on a 72-hour fentanyl patch, along with oxycodone 5 mg every four hours for breakthrough pain and a laxative to prevent constipation. The new care plan reduced her pain and anxiety.

Elizabeth initially did well on the phase 1 trial, completing four cycles, but was readmitted for intractable nausea and vomiting, along with hydronephrosis. She was to be on study for an indeterminate number of cycles, or until she progressed. Her nausea was brought under control with IV ondansetron and hydration. She also had another bilateral stent replacement. When she was admitted, the APRN contacted the chaplaincy department, and a priest visited with Elizabeth. The APRN asked for a nutritional consultation for Elizabeth’s worsening anorexia. The oncologists advised Elizabeth that her disease had once again progressed and that there was no further anticancer treatment, but that palliative care should be continued.

Clinical social workers supported Elizabeth, and a family meeting was held for her and her loved ones to consider the goals of care. A referral for initial palliative care home intervention, with transition to hospice care, was made. Elizabeth died peacefully, free of pain, with her family at her bedside, and the hospice provided bereavement support.

**Clinical Implications**
The literature and the experiences to date with this study have demonstrated opportunities for oncology nurses to improve the care of patients on phase 1 clinical trials. Nurses can use the QOL model to guide their assessment of patients’ physical, psychological, social, and spiritual needs. Nurses are key to managing the symptoms of advanced disease, as well as new symptoms anticipated from study drugs. Nurses also play a vital role in communicating with these patients about their values and goals of care as they consider advance directives and treatment options beyond the phase 1 trial. In addition, opportunities exist for collaboration between clinical trial nurses, other oncology nurses, and palliative care teams to provide the most comprehensive care for these patients.

**Conclusion**
The intent of this study is to test the provision of quality palliative care for patients with solid tumors participating in phase 1 clinical trials. The integration of palliative care into clinical trial care can improve patients’ QOL by addressing physical symptoms and
psychological distress. In addition, the patient education sessions cover QOL domains, including physical, social, psychological, and spiritual well-being.

Supportive care referrals to social work, nutrition, and psychological services are designed to improve patients’ QOL. This palliative care intervention study builds on prior work, which showed positive outcomes for patients and family caregivers in a National Cancer Institute–supported study, Palliative Care for Quality of Life and Symptom Concerns in Lung Cancer (Ferrell et al., 2015; Sun, Grant, et al., 2015; Sun, Kim, et al., 2015). The current study can serve as a model for the benefit of providing palliative care concurrent with clinical trials, which is vital to preventing, treating, and curing cancer.

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