The Integration of Palliative Care and Oncology: the Evidence

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This article will review the overlap between palliative care and oncology and discuss the available evidence that true integration of palliative and oncology care provides patients with optimal oncology care.

The Intersection of Palliative Care and Oncology Care

FIGURE 1
The balance between anti-tumor therapy and palliative care

FIGURE 2
Symptoms across the trajectory

There is a role for palliative care across the continuum of cancer care. Broadly defined, palliative care refers to treatment that relieves symptoms. For the majority of patients, the diagnosis of cancer results from medical evaluation of symptomatic complaints. Symptom control should be the first cancer treatment. Unless symptoms are adequately controlled, the patient will suffer unnecessarily and decline physically as diagnostic studies and initial clinical evaluations are performed (Figure 1).[1] Unrelieved symptoms, especially those resulting in profound weakness and poor nutritional status, such as pain and nausea, negatively influence performance status. Given that performance status is an important prognostic factor in cancer therapy, relieving symptoms to improve performance status and the patient's ability to tolerate cancer treatment has a direct influence on cancer survival. The balance between palliative care and anticancer therapy changes across the continuum of disease as a function of response to therapy and disease progression (Figure 2).

Control of all symptoms of cancer and its therapy is accepted medical practice and represents a standard of care. It is unacceptable to relieve only some symptoms and inadequately control other symptoms of cancer and its treatment. The vast majority of oncologists have incorporated the significant advances in control of chemotherapy-related nausea into their medical practice. Reflecting the significance of quality of life (QOL) for patients undergoing chemotherapy, these advances have been included in federal and nationally recognized guidelines. Based on peer-reviewed literature and national consensus guidelines, oncologists recognize that failure to adequately pre-medicate a patient who receives chemotherapy would be a breach of accepted medical practice and ethics. National guidelines from federal agencies and national consensus panels also exist for other cancer-related symptoms, such as pain. Withholding medications, like analgesics, to adequately relieve cancer-related symptoms is as much a breach of accepted medical practice and ethics as withholding adequate anti-emetic therapy prior to the administration of
Symptom assessment is an essential skill for recognition of recurrent cancer. The development of new symptoms may be the first sign of recurrent or metastatic disease. Guidelines of the American Society of Clinical Oncology (ASCO) for follow-up of early stage breast cancer recommend history and physical examination as the primary mode of identification of recurrent and/or metastatic disease.[2] Thus, even in the non-metastatic cancer population, expert skills in symptom assessment and, other aspects of palliative care are a necessity. Palliative care, including basic symptom assessment and management, communication and decision-making skills, and knowledge about psychosocial and community services, for patients with diseases other than cancer is typically provided by primary care physicians.[3] For most patients with cancer, the medical oncologist assumes responsibility for coordination and management of care, including the delivery of more complex palliative care. By virtue of the nature of the cancer experience, oncologists must be familiar with the multiple domains that cause patients with cancer and their families to suffer. These areas of concern include not only management of the patients' cancer and comorbidities, but also the physical and practical issues of dealing with cancer. The oncologist must also respectfully understand patient and family psychological, social, and spiritual concerns surrounding grief and loss at the end-of-life. Depending on the available healthcare system and infrastructure, this secondary level of palliative care may be provided by the medical oncologist or a palliative care specialist. When the complex nature of symptoms and/or psychosocial issues exceeds the expertise of the medical oncologist, referral to a tertiary level of palliative care may be needed. Tertiary-level palliative care is provided by an interdisciplinary team of specialists, including a palliative medicine physician, nurse or nurse practitioner, social worker, and chaplain and/or grief counselor. While all levels of palliative care services are increasingly available in hospitals throughout the United States, these services are less readily accessible in the outpatient setting.

The Role of Chemotherapy in Symptom Palliation

Evidence addressing the benefit of palliative care for patients with metastatic cancer, with or without standard oncology care, is drawn from trials of best supportive care with or without chemotherapy and from trials of integrated care. Let us consider the available data on palliative care for advanced lung cancer, as this remains the leading cause of cancer-related death in the United States. Because non–small-cell lung cancer (NSCLC) accounts for approximately 87% of all new lung cancer diagnoses, we can focus specifically on this group, for whom data are most extensive.[4] Between January 1965 and November 2009, there were 17 randomized controlled trials comparing the effect of supportive care and chemotherapy vs supportive care alone for patients with advanced NSCLC.[5] All of these trials enrolled previously untreated patients. A meta-analysis addressed the impact of chemotherapy on survival and reported a significant benefit from the addition of chemotherapy (hazard ratio = 0.77; 95% confidence interval, 0.71 to 0.83; P < .0001).[6] This was equivalent to a relative increase in survival of 23%, an absolute improvement in survival of 9% at 12 months (increasing survival from 20% to 29%), and an absolute increase in median survival of 1.5 months. This effect did not appear to be influenced by the particular chemotherapy agents prescribed or the use of a single-agent vs a multidrug regimen. The outcome of more recent trials did not differ from outcomes of those published prior to 1995. It is worth noting that the cost of therapy relative to survival and QOL, often defined as quality-adjusted life-years (QALYs), was not included in this analysis. One of the major challenges in evaluating these results is that best supportive care in these trials was not clearly defined. In fact, there is no widely accepted definition of best supportive care, bringing the conclusions of these studies into question. The Liverpool Reviews and Implementation Group (LRIG), one of seven groups commissioned to undertake systematic reviews of clinical effectiveness and cost-effectiveness for the National Institute for Health and Clinical Excellence in the United Kingdom, set out to identify the clinical and economic factors associated with the availability and delivery of best supportive care for patients with lung cancer in published, randomized, controlled trials.[7] The LRIG identified 26 trials that compared best supportive care plus chemotherapy vs best supportive care alone for patients with lung cancer. In all 26 trials the chemotherapy was well described, but a definition of best supportive care was not available in 12 of the studies and it was briefly described in the remaining 14 studies. Not surprisingly, the definition of chemotherapy in the randomized, controlled trials clearly stated the dose, number of cycles, duration of treatment, and guidelines for treatment of adverse events.[8] The trials that included a description of best supportive care failed to define the supportive care that was delivered. Unlike the specifics of administration of chemotherapy, phrases such as “at the discretion of the attending
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physician” or “investigators were free to choose best supportive care” or “whichever therapy was judged to be appropriate by the physician” were used to indicate the therapy administered to the “control” group. The authors concluded that access to palliative care services within randomized, controlled trials is limited and/or unreported and, at the very least, is undefined. It is very unlikely that “best” supportive care was available to the majority of patients in these trials, as the palliative care training of oncology fellows and the knowledge base of oncologists has been demonstrated, even recently, to be inadequate.[9] One can assume then, that these trials, by and large, compared administration vs no administration of chemotherapy. It is important to state that these “studies” failed to follow the precepts of scientific investigation; no discretion was allowed in the experimental arm of the study, whereas absolute discretion was allowed in the control arm of the study. Furthermore, the institutional review board (IRB) and peer-review publication processes also failed to adhere to strict scientific principles, as they did not challenge the lack of uniformity in delivery of supportive care in the control arm of the study. These failures underscore the inadequate knowledge base among academic oncologists, who have trained the oncologists in practice, serve on IRBs, and perform most of the peer-review for publications.

TABLE 1
Best Supportive Care vs Standard Oncology Care + Best Supportive Care: Lung Cancer

Non–Small-Cell Lung Cancer: Symptom Relief and Chemotherapy

Chemotherapy improves survival of good-performance patients with metastatic NSCLC. What data are available regarding the impact of chemotherapy on QOL and symptom endpoints for patients with metastatic NSCLC? Trials from the last decade demonstrate improvement in survival and QOL for patients with lung cancer treated with a variety of single agents (Table 1).[8-14] The ability of chemotherapy to improve QOL in patients with advanced lung cancer has been demonstrated (see Table 2).[13-16] In general, the likelihood of symptom relief correlated with the likelihood of tumor response.[16] However, the percentage of patients with symptomatic improvement was about twice as high as that of patients who achieved objective responses.[14] Local symptoms, such as cough, pain, and dyspnea responded better to chemotherapy than systemic symptoms, such as malaise and cachexia. The duration of symptom relief in these trials is not reported consistently but ranges between about 1.5 and 3.5 months.[14]

The impact of gefitinib on quality of life of patients

Improvements in QOL and disease-related symptoms for patients with advanced NSCLC have been demonstrated from treatment with targeted therapies. Erlotinib (Tarceva), for example, led to significant symptom improvement in nearly half of the patients who received it.[17] Gefitinib (Iressa) improved symptoms in more than half of the patients in the IDEAL-2 trial, which enrolled 216 symptomatic patients with advanced NSCLC who had previously been treated with at least two prior chemotherapy regimens (see Figure 3).[18,19] In the IDEAL-2 trial, patients were randomized to two different doses of gefitinib, and the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire was used to evaluate symptomatic improvement. The investigators evaluated the relationship between the weekly LCS scores, which are calculated based...
on seven lung-cancer-specific questions in the FACT-L, and radiographic response and survival. The likelihood of symptomatic improvement correlated with radiographic response. Patients who achieved a partial response had a 90% and 100% improvement in symptoms at the 250-mg and 500-mg gefitinib doses, respectively, and those who had stable disease achieved 81% and 61% symptom improvement rates for the lower and higher doses, respectively. Patients who achieved symptomatic improvement had a greater survival than those who did not. The authors concluded that tumor response and symptom response were related, and that each predicts survival. Standard chemotherapy may provide not only a survival benefit, but symptom control as well.

**Integrated Palliative and Oncology Care**

*TABLE 3*

Health Care Utilization by Patients With Non–Small-Cell Lung Cancer WhoReceived Standard Care or Integrated Care

What does palliative care add to the equation? Integration of standard oncology care and early palliative care was recently evaluated in a prospective, randomized trial in patients with newly diagnosed advanced NSCLC.[20] This single-institution trial randomized 151 patients to receive standard oncology care plus or minus early palliative care. Standard oncology care included administration of anti-cancer therapy and routinely prescribed symptom management. Symptom management was not withheld from any patient in the standard-oncology-care group, but it was prescribed at the discretion of the physician. The standard-oncology-care group received symptom management comparable to that of the control groups in the previously described studies. The palliative care intervention consisted of a baseline evaluation by a palliative care specialist and an advanced practice nurse, with follow-up on an at least monthly basis. The average initial consultation by the palliative care team took 55 minutes, 20 of which were spent on symptom management, 15 on patient and family coping, and 10 on education about the illness.[21] Guidelines for the palliative care consultations were adapted from the National Consensus Project for Quality Palliative Care but were not otherwise defined. The primary outcome of the trial was QOL at 12 weeks, as measured by the Functional Assessment of Cancer Therapy–Lung Trial Outcome Index (FACT-LTOI), which combines the LCS with the physical and functional well-being subscales. Secondary endpoints included the mood of the patient and the types of therapy administered during end-of-life care. Patients were enrolled from a thoracic oncology clinic, and all of the thoracic medical oncologists in the clinic agreed to approach and enroll patients. There was no difference between patients who were enrolled on study and those who were not. Patients assigned to the palliative care plus standard-oncology-care arm had significantly improved QOL scores at 12 weeks, compared with the control group, who only received standard oncology care ($P = .04$). This was true in spite of the fact that 10 patients (14%) in the standard care arm received palliative care consultations for symptoms at the discretion of their treating oncologist. Furthermore, patient-reported depression was significantly lower in the palliative care plus standard-oncology-care group ($P = .01$) compared with the standard-oncology-care group, in spite of an equal number of prescriptions for antidepressants in the two groups. Integrated care led to an overall decrease in health resource utilization, as shown in Table 3. Aggressive end-of-life care, defined by chemotherapy within 14 days before death, lack of hospice care, or hospice admission 3 or fewer days before death, occurred less commonly in the patients receiving palliative care plus standard care (33%) vs those receiving standard care alone (54%). Patients in the combination arm were more likely to have their resuscitation preferences recorded in the chart, and there was a trend for longer length of stay in hospice in the combination arm. Despite receiving less-aggressive end-of-life care, patients assigned to early palliative care experienced a survival benefit compared with those assigned to standard care. Patients assigned to early, palliative care survived 2.7 months longer than those receiving standard oncology care alone ($P = .02$). Early palliative care in patients with metastatic NSCLC resulted in improved survival with less aggressive end-of-life care, and, perhaps most importantly, improved quality in their remaining life. To date, this is the only prospective, randomized trial that specifically addresses the question of chemotherapy plus or minus well-defined supportive care.
Evidence supporting the benefit of specialized palliative care is limited by methodological shortcomings such as high rates of attrition resulting in missing data that are often not accounted for in statistical analyses. Zimmerman et al performed a systematic review of randomized controlled clinical trials in which specialized palliative care was the intervention and for which outcomes of QOL, satisfaction with care, or economic costs were endpoints. Only 22 trials were identified that met these criteria.[22] Although methodological limitations were identified in all trials, the most consistent evidence of benefit was seen in regard to family satisfaction with care, and 4 of 13 studies demonstrated that patients derived a significant benefit from the palliative care intervention. The methodological challenges of research in palliative medicine were highlighted in a review by El-Jawahri and colleagues of the evidence for palliative care in patients with incurable illness.[23] In spite of the limitations imposed by these challenges, they identified 22 randomized trials that
evaluated the efficacy of various palliative care interventions to improve symptom control, QOL, satisfaction with care, and family caregiver outcomes. These studies tested a variety of interventions; only 8 of the 22 tested a clinical intervention that included care from palliative care specialists. QOL was improved and end-of-life outcomes were improved by a palliative care intervention in five of seven studies. Higgenson and Evans also recently reviewed the available evidence to support routine integration of palliative medicine into oncology care.[24] They conducted a systematic review of all randomized trials that compared standard care vs care delivered by a specialist palliative care team (consisting of two or more clinicians). They identified eight trials that met their inclusion criteria. Significant benefits from specialized palliative care were demonstrated in three of eight trials for QOL outcomes and symptom control.

Because suffering is multidimensional, palliative care must address each of the dimensions of suffering. To accomplish this, an interdisciplinary palliative care team focuses on the patient experience of illness across the trajectory of disease. Specialized palliative care includes comprehensive management of physical and psychological symptoms, spiritual support, assistance with practical issues, support for decision-making, and end-of-life care. One challenge moving forward in the field is the lack of trained physicians and advanced practice nurses to provide palliative care in a multitude of care settings. To fully evaluate the impact of specialized palliative care, the components of the intervention must be clearly defined and adequately measured. To date, the vast majority of palliative care studies enrolled patients with terminal disease that limited the potential prolonged impact of palliative care. The methodological challenges of these trials have been clearly delineated and addressed in recent trials. It is time to initiate investigations that will define the optimal management of symptoms for patients at every stage of cancer.

References:


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