Evaluation of Palliative Endpoints in Oncology Clinical Trials

Paul B. Jacobsen, PhD, and Michael A. Weitzner, MD

For patients with advanced cancer, the treatment goal of improving the quality of life may be as important as improving their quantity of life.

Background: In recent years, there has been a growing recognition that improvements in quality of life may be as important as improvements in quantity of life in patients with advanced cancer. With this goal in mind, many oncology trials now seek to evaluate palliative endpoints as well as disease progression and survival.

Methods: Methodologic advances and challenges in evaluating palliative endpoints in oncology clinical trials are reviewed.

Results: Valid and reliable self-report measures have been developed that permit evaluation of palliative endpoints. Issues to consider in conducting research on palliative endpoints include the selection of appropriate outcome measures, the number and timing of outcome assessments, and the handling of missing data.

Conclusions: The inclusion of palliative endpoints into clinical trials in oncology has the potential to advance clinical care by identifying chemotherapeutic agents that are effective in improving the quality of life of patients with advanced cancer.

Introduction

In most randomized clinical trials in oncology, the primary aim is to determine whether one treatment results in better survival than another treatment. In trials involving patients with advanced malignant disease, other endpoints besides survival may be of equal relevance and interest. Most patients with advanced disease suffer from symptoms that are distressing in nature and can interfere with their activities of daily living and other aspects of functioning. In these circumstances, improving quality of life may be as important as improving quantity of life. That is, a treatment may be considered effective and clinically useful if it results in significant palliative benefits even in the absence of significant survival benefits.

In recent years, a number of important methodologic advances have occurred in the evaluation of palliative endpoints in oncology clinical trials. This article reviews these advances and discusses some of the challenges inherent in evaluating the palliative benefits of chemotherapeutic agents. A detailed description of a recently published clinical trial of chemotherapy for advanced prostate cancer is provided in order to illustrate the evaluation of palliative endpoints.

Measurement of Palliative Endpoints

Palliative chemotherapy has been defined as “the use of antineoplastic medications to affect the cancer and to reduce the adverse signs and symptoms caused either directly or indirectly by the malignant disease process.” Accordingly, the primary goals of palliative treatment for advanced cancer are to temporarily control incurable disease (while producing minimal toxicity) and to maintain or improve the patient’s quality of life. Methods for evaluating disease response and treatment toxicity are familiar to most investigators. Although the specific methods vary across studies, evaluation of disease response and toxicity typically involves the use of criteria derived from objective clinical findings and/or clinician ratings. Likewise, the specific methods used to measure quality of life also vary across studies.

Two features characterize most forms of quality of life evaluation currently used in oncology clinical trials. First, it is generally recognized that quality of life is a multidimensional construct and is best measured using instruments that assess multiple domains of functioning and well-being. Consistent with this view, most quality of life instruments measure physical, social, and emotional aspects of functioning as well as common symptoms of cancer and its treatment (eg, pain, nausea, and fatigue). Second, there is general agreement that quality of life is a subjective phenomenon and that the patient is the best judge of his or her own quality of life. Indeed, studies have shown that considerable disparities exist between concurrent ratings of quality of life made by patients and their physicians. Accordingly, assessment of quality of life in oncology trials is typically performed using patient self-report questionnaires.

Two of the most widely used multidimensional quality of life instruments in oncology are the General Version of the Functional Assessment of Cancer Therapy (FACT-G) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30). The FACT-G (Version 4) is a 27-item measure. For each item, respondents indicate the rating that best applies to them. Seven items are rated yes or no for an unspecified time frame (eg, “Do you have any trouble taking a long walk?”). Twenty-one items are rated on a five-point rating scale (0 = not at all; 4 = very much) how true each statement has been for him or her during the past seven days (eg, “I have a lack of energy.”). The FACT-G yields a total score for overall quality of life as well as subscale scores for physical well-being, social/family well-being, emotional well-being, and functional well-being. The EORTC QLQ-C30 is a 30-item measure. For each item, respondents indicate the rating that best applies to them. Seven items are rated yes or no for an unspecified time frame (eg, “Do you have any trouble taking a long walk?”). Twenty-one items are rated on a four-point scale (1 = not at all; 4 = very much) for the past week (eg, “Were you tired?”), and two items are rated on a seven-point scale (1 = very poor; 7 = excellent) for the past week (eg, “How would you rate your overall quality of life?”). The EORTC QLQ-C30 yields scores for five functional scales (physical, role, cognitive, social, and emotional), three symptom scales (nausea, pain, and fatigue), and a global health and quality of life scale. The measure also yields single-item ratings of additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) as well as the perceived financial impact of the disease and its treatment. Both the FACT-G and the EORTC QLQ-C30 are adequately valid and reliable and can distinguish patients according to their performance status. A number of disease-specific modules (eg, breast, lung, and prostate) have been developed to supplement each of these core measures. These modules assess additional symptoms and quality of life issues that are relatively specific to certain forms of cancer.
Linear Analogue Self-Assessment (LASA) scales are also widely used in quality of life research in oncology. A LASA scale consists of a 100-mm line with descriptors at each extreme. Respondents mark their current status somewhere along the line, and scores are obtained by measuring the distance in millimeters from the lower extreme (0 point) to the patient’s mark. LASA scales have been developed to measure a variety of symptoms (eg, pain) and aspects of functioning (eg, physical activity) as well as overall quality of life. These measures are popular partly because they are relatively easy and quick to administer. Moreover, there is evidence to suggest many LASA scales compare favorably with more established quality of life measures in terms of both their validity and their ability to detect changes over time. Although the use of LASA scales is appealing, caution is advised. Investigators need to determine whether the specific set of LASA scales to be administered has been validated for its intended use. In the absence of existing validity data, LASA scales should be used in combination with more established quality of life measures (eg, FACT-G, EORTC QLQ-C30) in order to establish validity.

**Methodologic Issues in the Evaluation of Palliative Endpoints**

There are several important methodologic issues to consider in evaluating palliative endpoints in an oncology clinical trial. Perhaps the most important issue is the selection of outcome measures. In addition to measures of disease response and treatment toxicity, a clinical trial evaluating palliative endpoints should include quality of life measures in order to capture the impact of treatment on a patient’s well-being and functioning. In most instances, the use of a well-validated multidimensional self-report quality of life instrument (eg, FACT-G, EORTC QLQ-C30) will meet this requirement. Of note, the EORTC QLQ-C30 has recently been shown to be sensitive to change among patients receiving palliative treatment for advanced cancer. Depending on the nature of the trial, it may be necessary to supplement these core measures with additional measures that provide more information about those symptoms that are most relevant to the patient population under study. For example, the lung module for Functional Assessment of Cancer Therapy (FACT-L) includes several items assessing respiratory difficulties. Likewise, in trials where relief of pain is a primary goal, it may be useful to collect additional information about the subjective experience of pain using a LASA scale or a multi-item measure such as the Brief Pain Inventory.

The number and timing of quality of life assessments are also important issues to consider. The desire to collect self-report information at relatively brief intervals in order to increase the likelihood of detecting changes over time must be weighed against concerns about the burden to patients and the financial cost of conducting frequent assessments. Osoba has proposed a set of guidelines that may be useful in determining the timing of quality of life assessments in clinical trials of palliative therapy. A baseline assessment of quality of life that is carried out before the initiation of treatment is necessary for two reasons. First, in randomized trials, the baseline assessment will indicate whether there are preexisting differences in quality of life between patients in the various treatment arms; if present, these differences would need to be adjusted statistically in order to accurately determine treatment effects. Second, the baseline assessment conducted prior to intervention provides an essential point of reference for identifying changes over time that may be attributable to the treatment under investigation. In most instances, one or more on-treatment assessments are also necessary. As noted by Osoba, the frequency and timing of these assessments will depend on the research question(s) being asked. For example, if the goal is to determine whether chemotherapy improves quality of life in patients experiencing disease-related symptoms (eg, pain), on-treatment assessments should be conducted just before the start of subsequent chemotherapy cycles in order to reduce the likelihood that results will reflect short-term treatment side effects. In instances where multiple chemotherapy cycles are being administered, the nature of the research question being asked and the financial costs of data collection will determine whether on-treatment assessments are conducted after each cycle or at less frequent intervals. Finally, there is the issue of off-treatment assessments (ie, assessments conducted following the completion or cessation of treatment). Once again, the nature of the research question and issues of cost will be the primary factors determining the number and timing of these assessments. In studies of patients with advanced disease (and a poor prognosis for survival), it may be both desirable and feasible to follow patients until disease progression occurs or even until death. Data collected during the off-treatment period would indicate if and for how long any of the observed on-treatment benefits to quality of life may have persisted.

A third important methodologic issue to consider is the handling of missing data. This issue is of particular relevance to studies of palliative endpoints. As Moinpour has noted, “In the very setting where quality of life questions are most compelling, they are the most difficult to evaluate because the missing data mechanism is often dependent on the very outcome being assessed — the health status and quality of life of the patient.” That is, patients who are experiencing negative health outcomes (eg, treatment toxicity, progressive disease, death) are also most likely to have missing quality of life data. Under these circumstances, analyses based on nonmissing data may lead to erroneous conclusions. For example, if quality of life data are missing on a consistent basis due to treatment toxicity, the analysis of only nonmissing data is likely to lead to an overestimate of the actual palliative benefits of the agent under study. At present, there is no consensus as to the optimal method for dealing with nonrandom missing quality of life data in clinical trials. As a general strategy, Fairclough and colleagues suggest that two questions be considered in attempting to evaluate the impact of missing data. First, why are the data missing? If data are missing for reasons related to treatment toxicity or disease progression, then the missing data mechanism is “non-ignorable” and statistical models appropriate for this situation should be explored. Second, how sensitive are the study results to different assumptions about the missing data mechanism? In the absence of a consensus as to the “best” approach, it is recommended that sensitivity analyses be performed to examine the effects of different methods of handling missing data. Additional information concerning the handling of missing quality of life data in oncology clinical trials is available in a special issue of *Statistics in Medicine* devoted to this topic.

**Example of the Evaluation of Palliative Endpoints**

In this section, we describe a published clinical trial of chemotherapy for advanced prostate cancer conducted by Tannock and colleagues. This study was selected for review because it represents a sophisticated methodologic approach to the evaluation of palliative endpoints. Systemic therapy for hormone-resistant prostate cancer has not been demonstrated to consistently increase overall survival. Estimated median survival for patients with this disease is six to 12 months. During this period, many patients experience moderate to severe disability due to bone metastases and require narcotic analgesics to achieve adequate pain control. The use of chemotherapy to provide palliation to this patient population is controversial. Most patients with advanced prostate cancer are elderly and may tolerate chemotherapy poorly due to concurrent medical conditions. Despite these considerations, several retrospective studies have been reported in the literature demonstrating a survival advantage among patients receiving chemotherapy. For example, an arm of the PACE (Prostate and Aggressive Cancer placebo-controlled evaluation) arm of the trial demonstrated a survival benefit among patients receiving chemotherapy. Based on these findings, Tannock and colleagues designed a randomized trial to test the hypothesis that treatment with mitoxantrone plus prednisone would provide better palliation than prednisone alone.

The study included 161 men with hormone-resistant prostate cancer at 11 Canadian institutions. Following randomization, all patients received 5 mg of oral prednisone twice daily. Patients randomized to combined treatment also received an initial dose of mitoxantrone (12 mg/m²) by intravenous injection. Additional chemotherapy was administered at three-week intervals with dose modifications based on nadir blood cell counts. Patients who were nonresponding or had progressive symptoms after six or more weeks of treatment with prednisone alone had mitoxantrone added to their treatment regimen.

Of principal interest here is the methodology used in the assessment of outcomes. Quality of life and toxicity data were collected in the clinic at three-week intervals. For patients receiving mitoxantrone plus prednisone, these assessments appear to have occurred just before the start of each treatment cycle. Pain relief was selected as the primary indicator of palliation. As part of the assessment of pain relief, patients completed the Present Pain Intensity (PPI) Scale of the McGill Melzack Pain Questionnaire. Specifically, patients rated their pain severity for the previous 24 hours on a six-point scale (0 = no pain; 1 = mild pain; 2 = discomforting pain; 3 = distressing pain; 4 = horrible pain; and 5 = excruciating pain). To measure analgesic use during the previous week, patients also kept diaries of their daily medication intake. An average daily analgesic use score was derived by counting standard doses of nonnarcotic medications as 1 unit and standard doses of narcotic analgesics as 2 units. These data were used to determine if patients met a primary criterion of the secondary criteria for a palliative response. The primary criterion consisted of the occurrence of a two-point reduction in the six-point pain intensity rating in the absence of an increase in analgesic intake. The secondary criterion consisted of a 50% reduction in the analgesic score in the absence of an increase in pain. Each criterion had to be maintained for at least 3 weeks in order to qualify as a palliative response. These criteria represent an innovative attempt to capture the complex relations between changes in pain severity and analgesic use that may constitute palliation. Although the criteria are reasonable, they do not provide an explanation of how the criteria were selected or evidence that changes of this magnitude are clinically significant. It should also be noted that one of the measures of pain relief (PPI) covers a 24-hour period, whereas the other measure (analgesic intake) covers a seven-day period. Ideally, the two pain relief measures should reflect the same time period. In addition to these measures, patients completed the following quality of life instruments at each cycle: the FACT-G, EORTC QLQ-C30, and additional information about the subjective experience of pain using a LASA scale or a multi-item measure such as the Brief Pain Inventory.

Results indicated that the primary criterion of a palliative response was met by more patients who initially received mitoxantrone plus prednisone (29%) than prednisone alone (16%). Of note, the EORTC QLQ-C30 has recently been shown to be sensitive to change among patients receiving palliative treatment for advanced cancer.
The duration of the palliative response, as defined by the primary criterion, was also longer in the group receiving combination therapy than in the group receiving prednisone alone (median 43 vs 18 weeks, respectively, \(P<.0001\)). These results are illustrated in the Figure. Similar results were obtained when the secondary criterion was included in the definition of a palliative response.

**Changes in LASA scores and EORTC domains were examined for patients who completed two or more assessments (96% of sample). In order to account for the variable follow-up period, the investigators computed and analyzed a “median change” score and a “best change” score for each subject on each measure. The former score appears to represent the median change for differences between baseline and follow-up assessments, whereas the latter score appears to represent the maximum positive change between baseline and follow-up scores. Analyses of these scores revealed that patients initially receiving combined therapy reported significantly greater improvement \((P<.05)\) than patients receiving prednisone alone on the LASA and EORTC pain scales (median and best changes), the LASA mood scale (best change only), the LASA constellation scale (median and best changes) and the EORTC constipation scale (best change only). In contrast, there were no significant differences on either LASA or EORTC scales measuring physical functioning, social functioning, fatigue, appetite, urinary symptoms, overall well-being, or global quality of life.

The investigators have recently published the results of additional analyses of the quality of life data from this trial.25 Instead of comparing median and best change scores, these analyses sought to examine whether there were treatment-related differences in the persistence and duration of changes in quality of life. At the end of the first six weeks of treatment, few differences between the two treatment arms were evident. Relative to their baseline (pretreatment) scores, patients in both treatment groups reported significant \((P<.01)\) improvements in a number of domains, including social functioning, anorexia, the impact of pain on mobility, and global quality of life. After twelve weeks of treatment, however, patients still receiving prednisone did not exhibit any significant improvements \((P>.01)\) relative to their baseline scores. In contrast, patients still being treated with mitoxantrone plus prednisone showed significant improvements, relative to baseline scores, in physical, role, emotional, and social functioning, in global quality of life, and in reports of several symptoms (eg, pain, fatigue, and anorexia). A similar pattern of results was observed at 18 weeks. The duration of improvement for each treatment group was calculated by summing the duration of “clinically meaningful change” on each measure. This was defined as a 10-point increase on a 0-to-100 scale on at least two successive measurements. Consistent with the results on persistence of change, patients who received combined therapy exhibited a significantly \((P<.05)\) longer duration of improvement in social functioning, pain, insomnia, and drowsiness relative to patients treated with prednisone alone.

Additional results from the original report indicated that, although overall survival was longer in the combined therapy group, the difference between the two treatment arms was not statistically significant \((P=.27)\). Likewise, although patients receiving combined therapy evidenced a greater reduction in serum prostate-specific antigen levels, this difference was not statistically significant \((P=.11)\). Toxicity data suggested that combined therapy was well tolerated by most patients. Specifically, only nine instances of febrile neutropenia occurred among a total of 130 patients (including crossovers) who were given 796 courses of mitoxantrone. In addition, only five cases of cardiac abnormality were possibly related to mitoxantrone use.

As noted above, the handling of missing data is an important methodologic issue in the evaluation of palliative endpoints. Information provided in the article suggests that the amount of quality of life data missing for patients who were seen for clinic visits was minimal. Pain severity data (PPI ratings) were obtained for 92% of clinic visits for the initial form of therapy, with no difference between the two treatment arms. Similar completion rates were reported for the other self-report measures. This high level of compliance with the collection of quality of life data is impressive, particularly for a multicenter study. The amount of quality of life data missing from patients who were not seen for clinic visits due to toxicity, morbidity, and mortality \(P<.01\) itself is complicated by the fact that patients who were nonresponding or had progressive symptoms after six or more weeks of treatment with prednisone alone had mitoxantrone added to their treatment regimen. The potential for this crossover feature to have a biasing effect on duration scores could not be evaluated in this clinical trial.

**Conclusions**

Patients with advanced cancer suffer from a variety of distressing symptoms that interfere with activities of daily living and other aspects of functioning. In recent years, there has been a growing recognition that improving the quality of life of these patients may be as important a treatment goal as improving their quantity of life. Accordingly, many randomized clinical oncology trials designed for patients with advanced disease now seek to evaluate palliative endpoints as well as disease progression and survival.26,27 The measurement of health-related quality of life is a central component of the evaluation of palliative benefits of chemotherapy treatment.

Quality of life is a complex construct that is best measured by using instruments that assess multiple aspects of functioning and well-being as viewed from the patient’s perspective. Reliable and valid multidimensional self-report quality of life measures have been developed that are sensitive to changes in health status among cancer patients with advanced disease. There are several important methodologic issues to consider in designing a clinical trial to evaluate palliative endpoints. These issues include the selection of measures relevant to the research questions, the determination of the number and timing of assessments during the course of the trial, and the handling of data missing due to toxicity, morbidity, and mortality. As illustrated by the clinical trial selected for review, the inclusion of palliative endpoints into clinical trials in oncology has the potential to add a meaningful quality of life component to clinical trials.
potential to advance clinical care by identifying chemotherapeutic agents that are effective in improving the quality of life of patients with advanced cancer.

References


From the Psychosocial Oncology Program at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.

Address reprint requests to Paul B. Jacobsen, PhD, Psychosocial Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Dr, Tampa, FL 33612.

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