Measuring Subjective Side Effects and Symptoms in Palliative Photodynamic Therapy

Teresa Goodell, PhD, RN, CNS, CCRN, APRN, BC

Purpose/Objectives: To evaluate the reliability and validity of the Photodynamic Therapy Side Effects and Symptoms Scale (PSES) and to begin to describe patient-reported outcomes of photodynamic therapy (PDT).

Design: Repeated-measures instrument validation. The PSES uses a 10-point numeric scale to evaluate side effects or symptom trouble or burden on 13 items.

Setting: A Pacific Northwest community hospital.

Sample: 14 patients with end-stage lung or esophageal cancer undergoing palliative PDT.

Methods: Participants completed five PSES surveys (i.e., at baseline and once a week for four weeks after PDT). Weekly phone calls were made to assess functional status, operationalized as Karnofsky Performance Status.

Main Research Variables: Symptoms and functional status.

Findings: The PSES possessed acceptable internal consistency reliability and concurrent validity. Functional status declined in the first week after PDT, concurrent with an increase in side-effect and symptom burden. Photosensitivity became more burdensome over time but was never extremely burdensome.

Conclusions: The feasibility of measuring a diverse set of side effects and symptoms in end-stage cancer with a single-page, large-type instrument essentially was supported. The study provided preliminary information about side effects and symptoms in patients undergoing palliative PDT.

Implications for Nursing: Nurses often are called on to provide information to patients considering various treatment options. This study offers the first data on patient-reported outcomes of palliative PDT that clinicians can use to help in answering inquiries. The design of the PSES may be replicated by researchers working with other populations with end-stage disease to reduce respondent burden and decrease attrition.

Key Points . . .

- Tumor reduction has been achieved with photodynamic therapy (PDT), an endoscopic treatment for palliation of malignant dysphagia or dyspnea, but no patient-reported outcomes of this treatment appear in the literature.
- An instrument was developed to measure patient-reported trouble or burden from symptoms and side effects associated with palliative PDT for esophageal and lung cancer.

Photodynamic therapy (PDT) is an endoscopic technique that involves the administration of a light-activated drug with subsequent exposure to wavelength-specific light, usually from a medical laser, to incite the formation of singlet oxygen and other reactive oxygen species to kill tumors. It was approved by the U.S. Food and Drug Administration for palliative use in 1996 for esophageal cancer and in 1998 for lung cancer. Palliative PDT relieves two major symptoms: dysphagia in obstructive esophageal cancer and dyspnea in obstructive lung cancer (Bruce, 2001). Objective safety and efficacy are well documented for palliative PDT for these indications (Diaz-Jimenez et al., 1999; Heier, Rothman, Heier, & Rosenthal, 1995; Lightdale et al., 1995; McCaughan et al., 1996; Moghissi, Dixon, Hudson, Stringer, & Brown, 1997; Moghissi et al., 1999). The patient outcomes evaluated in preapproval trials were performance status, tumor response, luminal diameter, dysphagia grade, and survival. Although PDT can offer rapid relief of obstruction, it carries potentially troublesome side effects, particularly intense ocular and cutaneous photosensitivity that may continue for as many as 10 weeks. Patients must remain indoors during daylight hours, avoid windows and skylights, and wear sunglasses and protective clothing outdoors for at least 30 days.

Clinical observations of people with late-stage cancer who have undergone PDT provided the impetus for studying the timing and magnitude of PDT-related side effects. Observed side effects and symptoms included worsening dysphagia, pain, and shortness of breath soon after treatment. The effect of prolonged, severe photosensitivity on quality of life,

Teresa Goodell, PhD, RN, CNS, CCRN, APRN, BC, is an assistant professor in the School of Nursing at Oregon Health and Science University in Portland. *The study was funded by the Society of Gastroenterology Nurses and Associates and the ONS Foundation. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the* Oncology Nursing Forum *or the Oncology Nursing Society. (Submitted March 2005. Accepted for publication October 3, 2005.)*

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especially in people with a limited life span, also was a concern. Although clinical trials evaluating objective outcomes of PDT exist, no accounts of patient experiences were found and no instruments have been developed to evaluate the diverse set of side effects and symptoms associated with palliative PDT for esophageal and lung cancer. The need for instrument development and evaluation from patients' perspectives thus arose.

Background and Significance

Photodynamic Therapy

The tool's design was driven by the nature of the population, previous clinical experience with palliative PDT, and the uniqueness of the treatment. PDT is a three-step treatment, usually performed on an outpatient basis. The first step is administration of a photosensitizing drug that is inert until exposed to light. After approximately 48 hours, the drug is largely excreted from most cells but is retained in malignant tumors as well as in liver, spleen, and skin cells. In the second step, tumors are endoscopically exposed to nonthermal laser light delivered through an optical fiber. The interaction of the light and drug forms reactive oxygen species, causing cell death by photooxidation, apoptosis, and tumor vascular thrombosis (Webber, Herman, Kessel, & Fromm, 2000). The third step occurs 24–48 hours later when the necrotic tumor is debrided. A second light exposure may be performed at that time, and subsequent repeated debridement may be required. The only photosensitizer approved for cancer PDT in the United States is porfimer sodium (Photofrin®, Axcan Pharma, Birmingham, AL). Common side effects of palliative PDT in obstructive esophageal cancer are pleural effusion, anemia, fever, nausea, constipation, overall body pain, chest pain, and abdominal pain. In obstructing lung cancer, two side effects occurred in more than 20% of patients: photosensitivity reactions (21%) and dyspnea (30%) (Axcan Pharma, 2004).

Methods

The current study was a repeated-measures evaluation conducted at an urban community medical center. Respondents completed a paper-and-pencil baseline tool before the first light exposure and follow-up tools weekly for four weeks. During the study period, 14 people were treated with palliative PDT. The principal investigator was the clinical nurse specialist and coordinator of the PDT program. The study was approved by an institutional review board, and consent for study participation was obtained from the patients.

Instruments

The **Photodynamic Therapy Side Effects and Symptoms Scale (PSES)** measures PDT side effects, other common cancer symptoms such as fatigue and depression, and symptoms expected to improve with PDT, such as swallowing. A 0–10 numeric scale is used to evaluate trouble or burden from pain, fatigue, nausea, depression, anxiety, swallowing, drowsiness, appetite, quality of life, shortness of breath, photosensitivity precautions, constipation, and a symptom that respondents may write in. Trouble or burden from photosensitivity precautions, not photosensitivity itself, was measured because people undergoing PDT do not test their photosensitivity until 30 days after treatment; strict precautions to avoid light exposure also were expected to affect them, not the degree of photosensitivity.

In addition to the PSES, **Karnofsky Performance Status (KPS)** (Karnofsky & Burchenal, 1949), the **Short Form-12 (SF-12)** (Ware, Kosinski, & Keller, 1996), and a 0–5 **dysphagia scale** were used throughout the study. KPS ranges from 0–100, with higher ratings signifying better function. Dysphagia grades range from 0–5, with lower ratings indicating better swallowing ability. The SF-12 is a general health status measure that provides physical and mental summary scores; higher scores denote better general health.

The disease severity in the population mandated limited measurement of symptom relief and side effects, which were operationalized collectively as symptom trouble or burden. Symptom trouble or burden is the respondent's self-defined trouble or burden from a symptom or side effect, which may include intensity, frequency, management difficulty, treatment mastery, meaning, effect on daily life, and other aspects of the side-effect and symptom experience as viewed by the patient. This broad conceptualization was chosen so that a diverse set of side effects and symptoms could be measured with a simple, large-type, single-page tool that could be completed easily by participants.

Results

Sample

All patients undergoing palliative PDT for esophageal (n = 10) or lung or airway (n = 4) cancer were asked to participate in the study. No potential participants declined to enroll, but one failed to return the questionnaires and several returned incomplete data. Eleven of the 13 participants who returned at least partial data were male, with a median age of 73 years. Median survival after PDT was 31 days, ranging from 18–266 days.

Instrument Reliability and Validity

Cronbach's alpha for the PSES was 0.87. Content validity was affirmed by review with three PDT physician providers, a biophysicist with PDT expertise, and a group of RNs involved in PDT at another center.

Spearman's rho correlations between KPS and the sum of the PSES items were in the expected direction and significant ($r_s = -0.54$, $p < 0.01$). Spearman's rho correlations among the PSES and SF-12 items all were in the expected direction, which supports the validity of measuring symptom trouble or burden from negative (e.g., pain, tiredness) and positive (e.g., quality of life, appetite) items simultaneously.

Some expected correlations did not achieve significance, such as the PSES and SF-12 pain items, which may be because they measure conceptually different pain information. The SF-12 pain item asks about the degree to which pain interfered with normal work, whereas the PSES asks how much trouble or burden the pain imposed. In the study population, normal work may be irrelevant; therefore, the SF-12 may not be as sensitive to the effects of pain as the PSES.

Similarly, dysphagia grade and PSES swallowing trouble or burden scores were not correlated, which may be related to the restriction of range in the dysphagia grade scores (Nunnally & Bernstein, 1994), where only 1 of 12 scores was greater than 1. PSES swallowing trouble or burden scores ranged from 1.5–10 ($\bar{X} = 4.1$, SD = 2.5). No score of 0 for swallowing trouble or burden was found on the PSES, but five scores

of 0 did appear on the dysphagia grade. Perhaps participants reported pain with swallowing, which is not measured by the dysphagia scale. However, if participants were able to swallow a certain food, albeit painfully, they met the criterion for that score. The PSES item may have permitted respondents to consider pain associated with swallowing, not just swallowing ability; therefore, operationalizing swallowing as trouble or burden, as in the PSES, may improve sensitivity to the range of dysphagia's effects in this population.

Symptom and Side-Effect Patterns

Studies of PDT prior to U.S. Food and Drug Administration approval measured dysphagia grade and KPS. In the current study, the measures were used to monitor patient outcomes prior to the development of the PSES. The dysphagia grade and KPS measurement were continued during tool development to evaluate concurrent validity.

The dysphagia grade improved at one week in patients with esophageal cancer, as shown in the preapproval studies. The differences from baseline at one and four weeks were statistically significant (Wilcoxon rank sum, $p < 0.05$). KPS decreased one week after palliative PDT (Wilcoxon rank sum, $p < 0.05$) but returned to baseline within one month.

Figures 1 and 2 show symptom and side-effect patterns over time in people with esophageal cancer as measured with the PSES. Eight participants returned complete tools at baseline, six at week 1, and four or five at weeks 2, 3, and 4. The small samples strictly limit conclusions about individual symptoms, but Figures 1 and 2 do suggest a trend toward worsening global symptom burden in the first week after PDT, which appears to decline thereafter. Increasing overall symptom trouble or burden in week 1 would explain the drop in KPS observed in the larger sample. The figures also reveal the variability and range of scores, suggesting that the symptoms measured by the PSES are relevant and variable in this population.

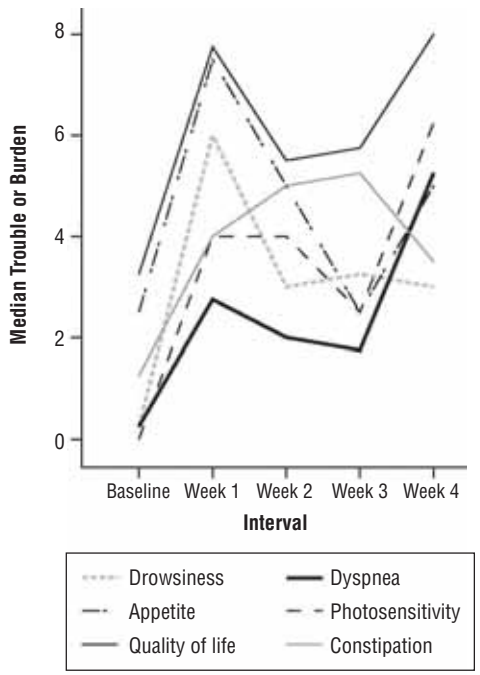

Figure 1. Median Scores on First Six Photodynamic Therapy Side Effects and Symptoms Scale Items Over Time

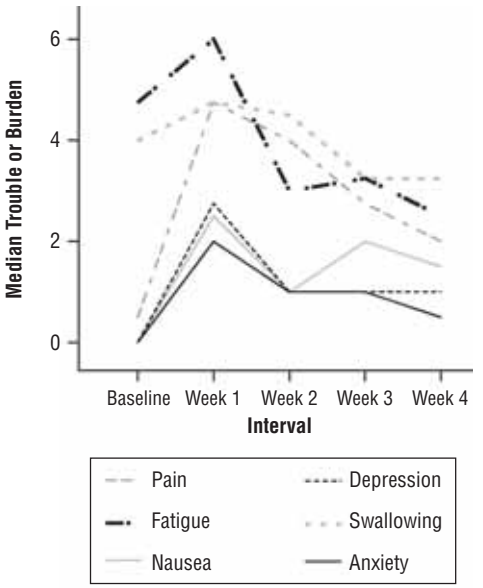

Figure 2. Median Scores on Second Six Photodynamic Therapy Side Effects and Symptoms Scale Items Over Time

Photosensitivity

Prolonged, intense photosensitivity is a unique side effect of PDT that has the potential to impair quality of life, regardless of cancer location. Responses from the current study's population of patients with esophageal or lung cancer were combined to observe trends in photosensitivity burden over time. Median trouble or burden associated with photosensitivity precautions in the sample (i.e., in six patients who supplied complete data at all intervals) increased from 0 to 5 during the four-week period, suggesting that individuals with late-stage cancer found photosensitivity precautions somewhat, but not extremely, troublesome.

Study Limitations

The current study experienced some common problems that may threaten the validity of research in patients with late-stage cancer, particularly longitudinal research. Despite making weekly phone calls and offering participants three options for completing the surveys (i.e., telephone, home visits, or independently), attrition was considerable. The major reason for attrition was declining health or death; however, this finding was not universal because some people completed the survey shortly before their deaths. The reason for attrition threatens the validity of the study and may have decreased symptom burden scores because the most symptomatic individuals may have been the least able to complete the study. Even though all candidates for the study agreed to participate, the number of eligible participants declined as a result of the decreased frequency of palliative PDT procedures at the study site over the course of the study. In addition, PDT was a relatively new treatment at the time of the study and often was reserved for use only after other options had been exhausted; therefore, study participants frequently were quite debilitated.

Combined, the factors reduced the recruitment and retention in the study and highlighted some of the issues inherent in conducting research with very seriously ill people with late-stage cancer. Other options for conducting this type of research include obtaining proxy reports from caregivers, reducing the number of reporting intervals, and enrolling at multiple study sites. The alternatives carry disadvantages of their own, such as greater cost and less reliable data. Despite such difficulties, research must continue to attempt to gain the perspective of people undergoing palliative cancer treatments, particularly when new treatments are introduced to clinical practice.

Nursing Implications

Oncology nurses frequently are asked for advice about the many treatment options available to patients; therefore, knowledge of the potential benefits and disadvantages of various therapies is critical for nurses. The findings of the current study provide nurses and other clinicians with preliminary information about the side effects of PDT as reported by patients, where none previously existed. Nurses may use the information to inform people considering PDT of its potential to relieve dysphagia while causing short-term decreases in performance status that appear related to increases in a variety of symptoms and side effects after PDT.

Clinicians involved in palliative PDT should be aware that symptoms and side effects may worsen in the week after PDT and should educate patients and their families about these potential effects. Knowledge of PDT-associated symptoms and side effects will allow practitioners to anticipate and proactively manage patients.

Additionally, the format of the PSES may be replicated by other researchers in situations where limited symptom and side-effect measurement is required. The tool may be suitable for use in clinical practice, but this has not yet been studied.

Conclusions

Although the small sample size limits the generalizability of the study findings, preliminary support was provided for the reliability and validity of the PSES, and trends in side effects and symptom relief were noted. The increase in burden from an array of varying symptoms and side effects, with a concurrent drop in performance status, was consistent with clinical observations of patients with esophageal or lung cancer.

The importance of limited measurement of side effects and symptoms in this population was clear. People with late-stage esophageal or lung cancer are known to be highly symptomatic and may be reluctant to participate in descriptive research that does not alter disease progression or improve quality of life. Using a single, consistent scale of symptom trouble or burden provided a feasible method of measuring the diverse set of unique symptoms and side effects of palliative PDT. The preliminary findings of this small study should be extended in future research with this population.

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Author Contact: Teresa Goodell, PhD, RN, CNS, CCRN, APRN, BC, can be reached at goodellt@ohsu.edu, with copy to editor at ONFEditor@ons.org.

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