

Patient-Reported Outcomes in Phase II Cancer Clinical Trials: Lessons Learned and Future Directions

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A B S T R A C T

With increasing limits on the resources available to conduct cancer clinical trials, the inclusion of patient-reported outcomes (PROs) in treatment and symptom management trials must be prioritized. Although it has been suggested on occasion that phase III trials should take precedence over phase II trials, we argue that there is a clear and important role for PRO assessment in phase II trials going forward. To illustrate the value realized from including PROs in phase II trials, we provide case examples from cancer treatment and supportive care. The benefits of including PROs in symptom management intervention research are exemplified using phase II trials targeting cognitive impairment. The inclusion of PROs in phase II cancer clinical trials adds important information about the impact of treatment in health-related quality of life, and advances the science of PRO measurement. These contributions significantly enhance the design of phase III trials, ultimately leading to the efficient utilization of clinical trial resources.

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INTRODUCTION

The inclusion of patient-reported outcomes (PROs) in phase II cancer clinical trials can yield valuable information about the impact of treatment and patient well-being throughout, and subsequent to, anticancer treatments. Available resources to support the study of PROs in phase II trials are relatively scarce and diminishing, so justification of the rationale and benefits realized from including PROs in oncology phase II studies is important. There are at least three specific reasons one would want phase II PRO clinical trial data: (1) to evaluate a response to treatment in otherwise unmeasurable disease or when tumor response is not a reasonable surrogate for patient benefit; (2) To understand the impact of a (presumably) toxic therapy regimen on health-related quality of life (HRQL); and (3) to test PRO measurements for their feasibility, acceptability, reliability, and validity in the target population before investing major resources in a subsequent phase III study. When planned well, phase II studies that include PRO data can help several decision-makers in the drug and treatment development sequence. Government regulators can use the data to help decide whether to approve or disapprove a proposed new therapy. Clinicians can review published PRO data to help decide whether or not to use the new therapy in their patients. Payers can incorporate the data into decisions regarding terms of reimbursement. Finally, the clinical researcher can use phase II PRO data to inform decisions about whether to con-

tinue to study PROs as end points in new studies, and with what measures.

This article will focus on three topics relevant to the inclusion of PROs in phase II cancer clinical trials: (1) trials conducted through the Eastern Cooperative Oncology Group (ECOG) will be presented to illustrate some of the benefits and lessons learned from the inclusion of PROs in phase II cooperative group trials; (2) a novel use of phase III PRO research results to inform phase II studies, such as the controversial Gynecologic Oncology Group (GOG) trial of intravenous versus intraperitoneal chemotherapy for optimally debulked ovarian cancer, will be discussed; and (3) the role of phase II PRO evaluations in developing symptom management interventions targeting HRQL and cognitive function among patients with brain tumors will be described.

LESSONS LEARNED IN ECOG PHASE II STUDIES

The ECOG Patient Outcomes and Survivorship Committee has a long history of measuring PROs in phase II cancer trials. Protocol E2E93 examined an outpatient regimen of taxol and carboplatin for the treatment of suboptimally debulked epithelial carcinoma of the ovary. Trial end points included response rate, progression-free survival, toxicities, and HRQL among 56 women. Study participants received six cycles of chemotherapy every 4 weeks. The Functional Assessment of Cancer Therapy (FACT)-Ovarian (FACT-O¹) was administered at

registration, cycle 4 day 1, 4 weeks after cycle 6 day 1, and 12 months postregistration. The response rate (complete response + partial response) was 72%.² Progression-free survival was 17.5 months for patients with measurable disease and 11.1 month for patients with nonmeasurable disease. The most common grade 3 or higher toxicities were leukopenia (26%) and granulocytopenia (74%). The primary objective for the HRQL study was to describe changes in HRQL over time in patients receiving this regimen. Greater than 50% of study participants demonstrated a clinically significant (10+ points) improvement on the FACT-O during and following treatment.² Compared with pretreatment baseline scores, median FACT-O scores were significantly higher during treatment ($P = .012$) and at treatment completion ($P = .006$), indicating improved HRQL associated with treating this typically responsive tumor. The physical well-being and functional well-being subscales of the FACT-O contributed to these improvements, further supporting the conclusion that this regimen was quite tolerable.

The inclusion of a PRO in this phase II trial helped support enthusiasm for this treatment regimen because it showed absence of HRQL decrement associated with chemotherapy toxicity. In fact, HRQL improved during treatment for most women. For patients with advanced ovarian cancer, treatment impact is not solely captured by response rate (CA-125) or progression-free survival, and the collection of PROs provided a comprehensive understanding of patients' experiences during and after treatment. In addition, the inclusion of a PRO in this phase II trial advanced the measurement of HRQL in ovarian cancer and helped to inform the development of the PRO assessment plan for a phase III trial.²

The phase II protocol E2399 was a function preservation trial that examined chemoradiotherapy for patients with resectable stage III or IV squamous cell carcinoma of the larynx or oropharynx. A total of 110 participants received two cycles of paclitaxel plus carboplatin, and patients who responded received an additional seven cycles of paclitaxel plus radiation therapy weekly. The FACT-Head and Neck (FACT-H & N³) was administered to participants before treatment, following induction therapy, and 3, 12 and 24 months postchemoradiation. Swallow function was assessed using the Dysphagia Outcome Severity Scale, a modified barium swallow, and the Functional Communication Measure, which was completed by a speech and language pathologist. Clinician-rated functional status was assessed using the Performance Status Scale for Head and Neck Cancer. Objective voice and swallow assessments were conducted before treatment and 3, 12, and 24 months postchemoradiation. The purpose of the function sparing technique is to leave functional status and HRQL intact; however, the risk of recurrence is increased with organ preservation. Therefore, the primary objective for the HRQL study was to determine if the function sparing technique truly did result in intact functional status and HRQL. Results demonstrated a marked decrease in swallowing at 3 months post-treatment with a return to baseline at 12 and 24 months.⁴ The Functional Communication Measure correlated with swallow questions from the FACT-H&N and the Performance Status Scale for Head and Neck Cancer. Correlations between patient- and clinician-reported function and physiologic function as measured by the Dysphagia Outcome Severity Scale were not significant. The inclusion of a PRO in this trial allowed the comparison of objective voice and swallow function to patient self-reported functional status. The lack of association between patient self-reported functional well-being and physiologic function supports the importance of including a PRO in this trial. The long-term assessment of patient HRQL has also

provided valuable data on patient functional status and well-being up to 2 years following chemoradiotherapy.

The protocol E4593 evaluated hyperfractionated accelerated radiation therapy for advanced, unresectable non-small-cell lung cancer. A total of 30 participants received radiotherapy days 0 through 4, 7 to 11, 14, and 15. The FACT-Lung (FACT-L; ⁵) was completed before treatment, at the end of treatment, and 4 weeks post-treatment. The primary HRQL objective was to document the trajectory of patient HRQL throughout radiotherapy for advanced unresectable non-small-cell lung cancer. HRQL results demonstrated that patient physical and functional well-being decreased during treatment, however 4 weeks post-treatment patient HRQL had returned to pretreatment levels.⁶ These data suggested that from a patient perspective there were no significant long-term detriments to HRQL from hyperfractionated accelerated radiotherapy. An additional benefit from including a PRO in this protocol was that it demonstrated the feasibility of administering the FACT-Lung in ECOG phase III lung cancer trials.

As illustrated by the three ECOG case studies discussed, the inclusion of PROs in phase II cancer clinical trials offers the following benefits: (1) patient-reported data on trajectory of symptoms and HRQL throughout treatment; (2) opportunity to advance measurement science through instrument development and testing; (3) help to inform development of PRO assessment plan for phase III trials and establishes feasibility of collecting PRO; (4) comparison of patient self-report to objective assessments; and (5) a sensitive measure of treatment-related toxicities.

We have learned, however, that not all PRO data from phase II trials are fully utilized, and we offer this case example to illustrate lessons learned from ECOG. E1493 was a phase II trial of sequential chemotherapy and radiotherapy for AIDS-related primary CNS lymphoma. Study participants completed one cycle of chemotherapy (cyclophosphamide, doxorubicin, vincristine, dexamethasone) with granulocyte colony-stimulating factor and external-beam whole-brain radiation therapy 7 to 10 days following chemotherapy. This trial was open to accrual for 3 years, which was the time required to meet the accrual goal of 35 participants. The Functional Assessment of HIV⁷ was administered to study participants before treatment, 1 month, 4 months, and 12 months post cycle 1 day 1, and at the time of progression. The HRQL objective was to evaluate whether patients experienced worsened HRQL due to treatment toxicities, of particular concern if no significant survival advantage was observed with treatment. Unfortunately, the PRO data from this trial were not analyzable due to high rates of missing data. Thus, the HRQL objective was not met. From this trial, we learned that a clear HRQL hypothesis and sufficient data quality are needed. HRQL data are not useful in the absence of a carefully planned study and well-implemented on-site data collection to minimize missing data. Long, slow-accruing studies have rippling negative effects on enthusiasm for the HRQL objective (as well as other objectives). Scientific progress outside the study can eclipse the significance of a slow-accruing trial.

ECOG phase II trials have illustrated the benefits and potential pitfalls for the inclusion of PROs in phase II cancer trials. ECOG trials have demonstrated how phase II trials can inform phase III trials. The following section will use a GOG case study to illustrate how PRO data from a phase III trial can help to inform the development of a phase II protocol.

THE GOG EXPERIENCE WITH PHASE II PRO STUDIES

Historically the GOG has incorporated HRQL end points into phase III clinical trials. One notable exception was a phase II trial of amifostine for prevention of peripheral neuropathy. In this trial of patients receiving cisplatin with 3-hour paclitaxel infusion, we aimed to determine whether there was sufficient evidence to support this agent to prevent the painful and often debilitating neuropathy associated with chemotherapy.⁸ PRO measurement (the 11-item FACT/GOG-NTX) was conducted along with an objective measure of touch sensitivity in the extremities (fingers and toes). Moore and colleagues⁸ reported that the self-reported PRO score change was a far better predictor of who needed to stop treatment due to neuropathy than the objective sensory measure. This clearly illustrated the need for patient-reported toxicity to help evaluate the place of amifostine therapy in neuropathy prevention.

Recent results of a provocative ovarian cancer trial have provided further basis for phase II PRO research. In an unusual reversal of the usual sequence from phase II to phase II research, the therapeutic setting of intraperitoneal chemotherapy is now moving from important phase II results back to the phase I and II setting. PRO results are central to the conclusions and debate in this period of transition. Results from the phase III study 172 of the GOG indicated that, compared to intravenous (IV) paclitaxel plus cisplatin, IV paclitaxel plus intraperitoneal (IP) cisplatin and paclitaxel improved survival in patients with optimally debulked stage III ovarian cancer by 15.9 months.⁹ This magnitude of improvement in median overall survival associated with IP/IV administration of chemotherapy has been considered similar to that observed with the introduction of cisplatin and paclitaxel in earlier decades. The difference in survival was sufficiently groundbreaking to motivate the National Cancer Institute to issue a rare Clinical Announcement.¹⁰ However, this treatment approach remains controversial, despite survival benefits, since there are technical challenges and adverse effects that are difficult to mitigate.¹¹ Consequently, the HRQL and PRO outcomes of this trial are considered key to the interpretation of this clinical trial, and are particularly informative to future trial designs.

In GOG 172, HRQL assessment was measured by the FACT-O,¹ the 11-item FACT-GOG/NTX,¹² and the FACT-GOG/Abdominal Discomfort measure.¹³ Assessment intervals occurred before randomization, before chemotherapy cycle 4, 3 to 6 weeks after chemotherapy cycle 6, and 12 months after the completion of cycle 6. HRQL was significantly worse in the IP group before cycle 4 and three to six weeks after treatment but not one year after treatment.⁹

Specifically, physical and functional well-being, and ovarian cancer symptoms were significantly worse in the IP arm before cycle 4 ($P < .001$) and 3 to 6 weeks post-treatment ($P = .001$ for FACT-Trial Outcome Index). Patients in the IP arm also reported significantly worse abdominal discomfort before cycle 4 ($P < .001$) and significantly worse neurotoxicity 3 to 6 weeks ($P = .001$) and 12 months ($P = .003$) after completing IP treatment.¹⁴ In short, during active treatment patients on the IP arm experienced more HRQL disruption, abdominal discomfort and neurotoxicity compared to those receiving conventional dose IV therapy. However, only neurotoxicity remained significantly greater for IP patients 12 months post-treatment. Importantly, both groups' quality of life improved over time.

Overall HRQL results⁹ and detailed PRO results¹⁴ have had a significant impact on future IP trial design. This influence is considered within the context of toxicities reported in this trial, since only 42% of patients in the IP arm were able to complete all six cycles of

assigned therapy, compared to 83% in the IV arm. Toxicities were associated with the presence of an IP catheter, IP administration of chemotherapy, or directly associated with chemotherapy.¹¹ As a likely result, fatigue, neurologic events, and pain were all significantly greater in the IP arm, as measured by Common Toxicity Criteria grades more than 3. The PRO results provided additional meaningful clinical information which not only illustrated overall improvement in HRQL over time despite treatment arm differences, but also reliably and validly illustrated outcomes of great concern in this trial (ie, abdominal discomfort and neurotoxicity).

For PROs to influence the development of the phase II IP study, the following information is recognized: (1) the IP regimen of GOG 172 used higher and more frequent dosing than the IV regimen, (2) toxicities were greater on the IP arm, (3) fewer patients on the IP arm were able to complete 6 cycles of therapy, (4) a statistically significant improvement in PFS and OS was evident for patients in the IP arm, and (5) the 65.6 month median survival on IP is the longest survival reported to date from an advanced OC randomized trial. Therefore, conclusions from this phase III trial noted that although patients who received higher dose IP therapy, compared to those with conventional dose IV therapy experienced more HRQL disruption, abdominal discomfort and neurotoxicity, they also experienced better recurrence-free and overall survival. Further, from baseline to 12 months after treatment, overall HRQL improved in both groups.

Taken together with the clinical trial results, the PRO data significantly influenced a proposed phase II trial design. The example of a phase II trial provided herein captures the significance of the phase III PRO results, and the potential for these results to influence the phase II end points. In a proposed randomized phase II trial of IP chemotherapy, the purpose of the study was to (1) determine the efficacy of three regimens in order to evaluate tolerability of regimens, defined as the proportion of participants completing six cycles of the assigned treatment, and (2) to compare treatment regimens on neuropathy, as measured by the FACT-GOG/NTX-4,¹⁵ the Abdominal Discomfort scale (FACT-GOG/AD,¹³ and the FACT-O-TOI.¹ In addition, this study would compare the three regimens on the proportion of patients requiring dose reductions or dose delays due to neuropathy, abdominal pain, metabolic or renal problems, nausea and vomiting, IP catheter failure, and to assess progression-free and overall survival. In this trial, HRQL assessment would occur before randomization, before cycles 2 to 6 and every 3 months for one year after treatment completion.

Intended to provide a more precise estimation of toxicity, the PRO contribution to the development of phase II IV/IP studies has been significant. As a result, PRO data incorporated into the phase II setting aim to support the development of a more acceptable yet still more clinically effective treatment alternative for administration of IP chemotherapy. It is noteworthy that as development of this protocol was underway, consideration of accrual termination could be based, in part, on the interim analyses of neurotoxicity of PROs during this trial. Fortunately, we have experience with this very approach from the Moore et al amifostine trial.⁸ The PROs outcomes of the phase III trial supported proposed development and evaluation of a randomized phase II study, where PROs continue to represent key study objectives.

THE WAKE FOREST RESEARCH BASE EXPERIENCE TARGETING COGNITIVE IMPAIRMENT

This section illustrates the role of PRO assessments to evaluate phase II symptom management trials targeting HRQL and cognitive function.

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Long-term survivors of partial or whole brain radiation therapy for primary or metastatic brain tumors often experience adverse sequelae of treatment that impact their HRQL, mood, and cognitive function. The patient's perspective is eloquently described by Mrs Susan T. Sontag, Vice President of the Sontag Foundation, a philanthropic organization with the primary focus of improving the lives of individuals with brain tumors, describes her symptoms 16 years following surgery, radiation therapy, and chemotherapy for a left temporal anaplastic astrocytoma as follows: "Everything I do is slow. I walk, talk and think slowly. And my brain doesn't work right. I still have no short term memory. That makes it frustrating and sometimes embarrassing for me. Much of the time I can't even remember the names of relatives and close friends. And I can walk from one room of our house to the other and arrive not knowing why I wanted to get there. I am always confused. Usually I feel as though I'm in a complete fog. And I often can't answer even simple questions. That makes it very difficult for me in social settings. Because I look normal and often sound normal, people assume I am normal. But I'm not. Everything is difficult for me. . . . I am less sure of myself. I'm more emotional. I cry a lot. And I get depressed a lot knowing that I will never have my competence back." (Sontag Foundation Distinguished Scientists Awards ceremony speech at the Society for Neuro-Oncology Meeting, Toronto, Canada, November 20, 2004.)

Shaw et al recently reported the results of a prospective, open-label phase II study of donepezil (Aricept; Pfizer, New York, NY), an US Food and Drug Administration approved reversible acetylcholinesterase inhibitor used to treat mild to moderate dementia of the Alzheimer's type,¹⁶⁻¹⁸ in a group of brain tumor patients who were six month or longer survivors of brain radiation therapy (RT)¹⁹. The major eligibility criteria included age \geq 18 years, life expectancy \geq 30 weeks, prior partial or whole brain RT \geq 6 months before enrollment, no imaging evidence of progressive brain disease in 3 months before enrollment, stable or decreasing steroid dose, Karnofsky Performance Status (KPS) \geq 70, and no planned brain tumor therapy during 30 week study period. Patients received donepezil 5 mg/d for 6 weeks, then 10 mg/d for 18 weeks, followed by a "washout" period of 6 weeks off drug. PROs included HRQL and mood. HRQL was measured with the FACT-Brain, which includes subscales for physical well-being, emotional functioning, social functioning, and functional well-being, as well as additional items specific to brain tumor patients, which measure brain-specific HRQL.²⁰ Mood was evaluated using the Profile of Mood States (POMS), which includes subscales for confusion, fatigue, depression, anxiety, anger, and vigor.²¹ Non-PROs included: (1) KPS²²; (2) Mini-Mental State Exam (MMSE)²³, a measure of global cognitive function; and (3) Specific tests of cognitive function, including attention and concentration, visual-constructional skills, executive function and memory.¹⁹ The FACT-Brain and POMS were patient self-administered, whereas all other tests were either physician assessed (KPS) or administered to patients by a trained and certified research nurse (MMSE and cognitive function tests). The assessment battery, which was given at baseline, 12, 24, and 30 weeks, required approximately 90 minutes to complete.

The full results of this study have been previously reported.¹⁹ The focus of this summary will be the PROs. Of 34 patients who initiated the study, 24 remained on study for 24 weeks and completed all PROs. The other 10 developed disease progression before the 24 week evalu-

ation point. All 24 patients had a primary brain tumor, mostly low-grade glioma. The mean age of the group was 45 years. Overall HRQL as measured by the FACT-Brain improved (ie, increased) from baseline to 24 weeks (mean scores 124 at baseline versus 134 at 24 weeks; $P = .07$). The emotional and social functioning subscales, as well as brain-specific HRQL were significantly improved ($P < .05$). Total score on the POMS also significantly improved (ie, decreased) from baseline to 24 weeks, indicating an improved mood (mean scores 47 at baseline versus 30 at 24 weeks; $P = .03$). The confusion, fatigue, and anger subscales of the POMS were also significantly improved ($P \leq .05$). Significant improvements were also seen in cognition,⁴ whereas the other non-PROs, KPS and MMSE, did not change. The most common toxicities were fatigue, insomnia, and diarrhea, and were rated as grade 1 (mild) in 81% of patients.

This open-label phase II study of a 24 week course of the acetylcholinesterase inhibitor donepezil in \geq 6 month survivors of brain RT demonstrated a significant improvement in the patient-reported outcomes of brain-specific HRQL and mood. Based on these results, a phase III double-blind, placebo-controlled study in brain irradiated long-term survivors is being conducted by the Community Clinical Oncology Program Research Bases of the Comprehensive Cancer Center of Wake Forest University and The University of Texas M.D. Anderson Cancer Center.

SUMMARY AND IMPLICATIONS

Using ECOG, GOG, and Wake Forest research base trials as case examples, we have discussed several potential benefits of including PROs in phase II cancer clinical treatment trials. Although resources to support PRO research are limited, we suggest that valuable lessons and contributing information are learned at the phase II level, and this can make phase II PRO research better informed. Some benefits of including PROs in selected phase II studies include the attainment of patient-reported data on the trajectory of symptoms and HRQL during a new treatment, the patient-reported impact of a new supportive therapy, the provision of a sensitive measure of treatment-related toxicities, establishment of the feasibility of collecting PRO data for phase III trials, the opportunity to compare objective findings with PRO data, and the advancement of measurement science through new instrument development and testing. One argument against the inclusion of PRO assessments is that many phase II trials are single arm trials. All of the above benefits can be realized regardless of the availability of PRO data from a control or comparison arm. To be maximally beneficial, a carefully planned PRO assessment strategy directed by a clear HRQL hypothesis is essential.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Manuscript writing: Lynne Wagner, Lari Wenzel, Edward Shaw, David Cella

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