Oral Anticancer Agents

An intervention to promote medication adherence and symptom management

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Oral anticancer agents (OAs) are now established as the best treatment modality for many types of cancer because of their superior effects (Bestvina et al., 2014; Greer et al., 2016). Use of OAs requires patient self-management of symptoms from side effects, as well as adherence to the medication regimen (Spoelstra et al., 2015). However, patients are known to experience severe symptoms and miss as many as one-third of the prescribed OA doses (Greer et al., 2016; Puts et al., 2014; Spoelstra et al., 2013).

OAs have been on the market for more than a decade; however, few trials have examined start-of-care procedures for patients on newly prescribed treatment. This article reports on a trial that examined an intervention (ADHERE) using motivational interviewing (MI), brief cognitive-behavioral therapy (CBT), and systematic patient education (PE) provided by nurse practitioners (NPs) to teach patients to self-manage symptoms and increase adherence to OAs.

Nonadherence to OAs is a significant clinical problem that may result in hospitalization, treatment failure, and reduced longevity (Greer et al., 2016; Puts et al., 2014). Factors known to influence adherence include race, gender, cancer type and stage, depression, motivation, and medication beliefs (Greer et al., 2016; Puts et al., 2014). The presence of coexisting comorbid conditions may also make self-management more difficult (Koroukian, Murray, & Madigan, 2006; Spoelstra et al., 2015).

The effectiveness of self-management in patients with cancer is well established (McCorkle et al., 2011). This includes motivating patients using MI, improving behaviors using CBT, and providing knowledge through PE (Conn, Hafdahl, Brown, & Brown, 2008; Ruppar, Conn, & Russell, 2008).

As described in Spoelstra, Burhenn, DeKoekkoek, and Schueller (2016), social cognitive theory underpinned the approach to improve self-efficacy (Bandura, 1977), and the information-motivation-behavioral skills model guided the intervention (Fisher, Fisher, Bryan, & Misovich, 2002).

Methods

Study aims were to (a) refine an NP-led ADHERE intervention to promote medication adherence and symptom management in adults with cancer newly prescribed OAs (phase 1) and (b) explore feasibility, preliminary efficacy with adherence and symptom severity, and patient satisfaction (phase 2).

Design

Phase 1 refined the ADHERE intervention using an iterative single-subject design, which has previously proven effective in practice-based research (Francis, 2005). The intervention was used with one patient and improved prior to use with the next patient. Phase 2 determined feasibility,
preliminary efficacy on adherence, symptom severity, and satisfaction using a quasiexperimental, longitudinal, sequential design over eight weeks. To prevent control group contamination, patients were enrolled in the control group first, followed by the intervention group.

Sample
Human subject committee approvals were obtained, and the trial was registered at ClinicalTrials.gov (Identifier NCT02337296). Participants were recruited from three community cancer centers. Inclusion criteria were being aged 21 years or older, having been prescribed an OA within the past 30 days, and being able to speak and read English. Those assessed with cognitive impairment were excluded. Phase 1 occurred at one clinic, whereas phase 2 occurred at two other clinics.

Study Procedures and Data Collection
Usual care was provided to all participants and consisted of instructions on the OA regimen (dosage and timing), common side effects, symptom management, ways to remember to take the OA (e.g., calendar, pill box), medication safety, and when to contact a provider. Baseline demographics, cancer site and stage, OA type and regimen, and days since initiation of OA were collected by recruiters. Trained staff conducted baseline telephone interviews (week 1), collecting data on sociodemographics, depressive symptoms, self-efficacy, and beliefs about medications; these interviews took, on average, 35 minutes.

Those in the intervention group had a face-to-face 30-minute session (week 1) with the NP in the clinic, followed by three weekly telephone calls with the NP (weeks 2, 3, and 4) (see Online Supplemental 1 and 2 of Spoelstra et al., 2016). The NP discussed medication adherence, symptom management, and safety tips, as well as provided a toolkit consisting of strategies to support self-management (Given et al., 2008). When patients identified a troublesome symptom, the NP selected strategies from the toolkit for them to try at home; telephone sessions included discussion of use of those strategies. Satisfaction with ADHERE was measured via telephone (week 5) using a survey the team developed (Spoelstra et al., 2013).

Phase 2 patients received weekly telephone calls (weeks 2–7) to assess OA adherence and symptom severity. Exit interviews (week 8) were conducted by telephone at study completion. Data were entered and stored in the web-based Patient-Reported Outcomes Measurement Information System (PROMIS) (www.assessmentcenter.net).

Data Analysis
Field notes were maintained in phase 1 and used to refine the semistructured scripts prior to enrollment of the next patient until the investigator determined that the script was finalized. In phase 2,

| TABLE 1. BASELINE SAMPLE CHARACTERISTICS IN PHASE 2 |
|----------------|----------------|----------------|
| CHARACTERISTIC | TOTAL SAMPLE (N = 54) | INTERVENTION (N = 24) | CONTROL (N = 30) |
| Age (years)    | 63.79 ± 13.18  | 64.26 ± 13.97  | 63.41 ± 12.75  | 0.82 |
| Summed symptom severity | 18.72 ± 18.33 | 14.55 ± 14.15 | 22 ± 20.71 | 0.16 |
| Total number of symptoms | 4.17 ± 2.96 | 3.61 ± 2.68 | 4.62 ± 3.14 | 0.22 |
| Complexity of dosing of oral agent | 0.54 | 0.9 | |
| Simple         | 18 | 7 | 11 |
| Complex        | 36 | 17 | 19 |
| Education      | 0.9 | | |
| High school or less | 20 | 9 | 11 |
| Some college/bachelor’s degree | 32 | 14 | 18 |
| Graduate degree | 2 | 1 | 1 |
| Ethnicity      | 0.58 | | |
| Hispanic or Latino | 1 | 1 | | |
| Not Hispanic or Latino | 53 | 23 | 30 |
| Gender         | 0.54 | | |
| Female         | 30 | 15 | 15 |
| Male           | 24 | 9 | 15 |
| Race*          | 0.99 | | |
| Caucasian      | 53 | 24 | 29 |
| Other          | 1 | | 1 |

*Because of small sample sizes, comparisons of proportions for each category were carried out using Fisher’s exact test.

Note. The possible range for summed symptom severity (total of all symptom scores) was 0–190.
frequencies, means, and standard deviations were calculated for the sample characteristics. Intervention feasibility was measured by discontinuations during treatment with OAs, the number of patients who accepted enrollment compared to those who declined participation, and the study completion percentage. Frequencies for responses to satisfaction items were tabulated. Intervention and control group sociodemographics, disease and treatment characteristics, and outcomes at baseline were compared. General linear models were used to relate postintervention outcomes by study group while adjusting for baseline values. Least square (LS) means were obtained from these models and compared by study group. Effect sizes (ESs) were estimated to gauge the magnitude of intervention effects. Linear mixed-effects models were used to analyze repeated measures of the number of symptoms and symptom severity during weeks 2–8 in relation to study group and while adjusting for baseline. The LS means of the number of symptoms and symptom severity at each week were estimated and compared by study group. Data analyses were performed using SAS®, version 9.4.

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### Results

Sixty-four patients were screened and eligible for the study, and 61 consented. Of those, 57 completed baseline interviews, and 40 completed weekly and exit surveys. Specific to the phase 2 intervention group, 25 patients were screened and eligible, and all 25 consented. Of these, 24 completed baseline interviews and the face-to-face ADHERE session, 18 completed three ADHERE telephone calls, and 17 completed weekly and exit surveys.

No group differences at baseline were found with respect to sociodemographics, OA type or dosing complexity, cancer site or stage, number or severity of symptoms, depression, self-efficacy, or beliefs about medications (see Table 1). Postintervention LS means and their standard errors adjusted for baseline values (except self-reported adherence) differed significantly by study group for both the number and summed severity of symptoms (for both, p < 0.01), with moderate effect sizes of 0.48 and 0.37, respectively (see Table 2). Medication self-efficacy was higher in the control group (p = 0.04, ES = 0.47). No other significant differences were observed between study groups postintervention, and the ESs were also small for all outcomes, including the total number of weeks in which patients reported adherence. To complement the analysis of postintervention outcomes, detailed week-by-week values for adherence and symptoms were summarized. Weekly self-reported medication adherence rates for the intervention and control groups ranged from 79%–100% adherence. Weekly comparisons of number and severity of symptoms favored the intervention group, with significance reached during weeks 2 and 5 (p = 0.03–0.05).

All 19 patients noted that they were satisfied with the content of the intervention (i.e., information regarding symptoms and adherence to cancer medication), as well as that it was helpful. Regarding the timing of the first office visit and weekly telephone calls, all 17 patients who answered the question...
said they were satisfied. In terms of management of symptoms at home, 16 of 17 who answered the question stated that ADHERE had helped in this regard, and 11 of 19 stated that the intervention helped with medication adherence (5 said it did not help, and 3 said it did neither). Of the 19 in the intervention group, 18 said they would recommend ADHERE to assist with medication adherence and symptom management. Seventeen of 19 said they would recommend ADHERE as a way for oncologists or nurses to help patients take their cancer pills.

Discussion
This study targeted a challenging clinical problem among patients with a life-threatening disease (Puts et al., 2014). Feasibility of the face-to-face ADHERE intervention was established with a high rate of completion. However, ADHERE telephone call completion was slightly less than expected (desired 80% completion but attained 72% completion). The three telephone calls may be more than needed or may need to be spread over more weeks. Patients newly prescribed an OA receiving ADHERE reported fewer symptoms, less severity of symptoms, and lower self-efficacy. Because of the interventions provided, patients may have realized the need to adhere to the complex medication regimen, whereas those in the control group may not have understood the OA complexity or details of care. Preliminary efficacy of the ADHERE intervention was demonstrated, intervention participants were highly satisfied, and the intervention is feasible as a standard of care for patients with cancer who have been newly prescribed OAs. Participants were also highly satisfied with the ADHERE intervention.

Limitations
Several limitations of this study need to be acknowledged. The sample size was relatively small. Adherence was measured by self-report, which may be inaccurate or biased. Weekly assessment telephone calls may have prompted adherence in both groups. Finally, randomization was not performed because of potential contamination within practice settings.

Conclusion
ADHERE may be feasible for standardizing clinical practice for patients newly prescribed OAs. ADHERE has high generalizability, as well as the potential to transform cancer care, and it may be modified for the self-management of other conditions. The number of patients with cancer who receive oral treatments are increasing, and this intervention may enable patients to self-manage their symptoms while adhering to their cancer regimen (Greer et al., 2016) and achieving the optimal therapeutic response (Puts et al., 2014; Spoelstra et al., 2013).

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