10-14-2022

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Recommended Citation

Sikorskii A, Given CW, Chang S, Tam S, Movsas B, and Given B. Patient reported outcomes and unscheduled health services use during oral anti-cancer treatment. J Pain Symptom Manage 2022.

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Brief Report

Patient Reported Outcomes and Unscheduled Health Services use During Oral Anti-Cancer Treatment

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Abstract

Context. People on oral anti-cancer agents must self-manage their symptoms with less interaction with oncology providers compared to infusion treatments. Symptoms and physical function are key patient-reported outcomes (PROs) and may lead to unscheduled health services uses (urgent care and emergency department [ED] visits, hospitalizations), which in turn lead to increased health care costs.

Objectives. To evaluate the prediction of unscheduled health services uses using age, sex, and comorbidity, then determine the extent to which PRO data (symptoms and functioning) improve that prediction.

Methods. This post-hoc exploratory analysis was based on data from the control group of a trial of medication adherence reminder and symptom self-management intervention for people starting a new oral anti-cancer agent (n = 117 analyzed). Severity and interference with daily life for 18 symptoms, physical function, and depressive symptoms were assessed at intake (oral agent start), and four, eight, and 12 weeks later. Unscheduled health services use during three four-week periods after the start of oral agents was analyzed using generalized mixed effects models in relation to age, sex, comorbidity, and PROs at the beginning of each time period.

Results. The summed severity index of 18 symptoms and physical function were significant predictors of hospitalizations in the four weeks following PRO assessment. The addition of PROs improved areas under the receiver operating characteristic curves to be over .70 in most time periods.

Conclusion. Monitoring of PROs has the potential of reducing unscheduled health services use if supportive care interventions are deployed based on their levels. J Pain Symptom Manage 2022;000:e1−e7. © *2022 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Cancer, Patient reported outcomes, Unscheduled health services use, Oral agents

Key Message

This brief report is devoted to the analysis of longitudinal data from the control group of a recently completed symptom management trial. The results indicate the usefulness of patient-reported outcomes in prediction of unscheduled health service uses in the following four weeks.

Introduction

Use of oral anti-cancer treatment has increased over the past decade for multiple sites of cancer.[1] In exchange for eliminating repeated trips and extended time in infusion units, survivors (defined as people from the time of diagnosis to end of life[2]) on oral agents must self-manage their symptoms (e.g., fatigue,

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Accepted for publication: 6 October 2022.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2022.10.003

depression, skin rash)[3] with fewer interactions with their oncology care team. Unmanaged symptoms can lead to unscheduled health services use (symptom-related oncology visits, urgent care and emergency department [ED] visits, hospitalizations), which in turn lead to increased health care costs. Symptoms are the number one driver of unscheduled health services use in both general and cancer populations,[4–6] and reductions in symptoms were associated with decreased hospitalizations and ED visits and decreased additional visits to the provider.[7,8] A series of longitudinal studies[9–12] found an association between increasing symptom prevalence and poorer physical and emotional functioning.

Symptoms and functioning are key patient-reported outcomes (PROs), and efforts to monitor PROs during cancer treatment have been made over the past decade. Trials of telephone symptom monitoring with reports to clinicians have improved quality of life and even survival,[13,14] but some resulted in no difference compared to the standard care.[15] While the literature supports the use of PROs as "vital signs" and predictors for cancer outcomes,[16,17] the optimal frequency of symptom monitoring and thresholds at which interventions should be deployed remain open questions.[18,19] Deployment of supportive care interventions could be based on various factors, one of which is prevention of unscheduled health services use. In this brief report, we evaluate the extent to which PROs (symptoms and functioning) predict subsequent unscheduled health services use over and above other predictors established in the literature.

Much of the evidence for predictors of unscheduled health services use is available from retrospective cohort studies and large databases from countries with a single payer system.[20,21] Among people with pancreatic cancer, admissions to the intensive care unit were predicted significantly by male sex, older age, living in urban areas, being married, having lower socio-economic status, and greater comorbidity.[22] Hospital readmissions were predicted by polypharmacy, comorbidities, therapy non-adherence, cognitive impairment, and older age were among people with chronic conditions.[23] In an ethnically diverse sample of cancer survivor undergoing chemotherapy or targeted therapy, younger age and availability of health insurance were key predictors of unscheduled health services use.[24] Using retrospective data, Patient Reported Outcome Measurement Information System (PROMIS) tools for anxiety, sleep disturbance, depression, fatigue, pain interference, physical function, and ability to participate in social roles did not improve the prediction of 90-day hospitalization beyond claim's data predictors of age, sex, county of residence, and comorbidity indices. [25] Based on this evidence, we performed an exploratory analysis of longitudinal data from the control group of a trial of supportive care intervention to evaluate the extent to which PRO data (symptoms and functioning) are important predictors of unscheduled health services use over and above age, sex, and comorbidity.

Methods

This post-hoc exploratory analysis was based on data from the control group of a trial of medication adherence reminder and symptom self-management intervention for patients starting a new oral anti-cancer agent other than aromatase inhibitors and tamoxifen for breast cancer. This clinical trial was registered with ClinicalTrials.gov (identifier NCT02043184). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The approvals for this trial were obtained from the Institutional Review Board of the investigators' University and participating sites. Informed consent was obtained from all study participants. Trial results were reported previously. Briefly, adherence was high and did not differ by study group; symptoms were reduced in the intervention group compared to control immediately post intervention.[26]

Sample

Between 2013 and 2017 survivors meeting the following inclusion criteria were recruited from six National Cancer Institute-designated Comprehensive Cancer Centers: 21 years of age or older; Eastern Cooperative Oncology Group (ECOG) score of 0−2 or Karnofsky score of ≥50; able to read and speak English; had a cellular or land line telephone; and prescribed any one of 28 FDA approved oral oncolytic agents for either curative or palliative intent. Recruiters at each site explained the study to potential participants and obtained an informed written consent.

Procedures

When survivors received an oral oncolytic agent and began taking it, the baseline telephone interview was conducted to assure that the start of the study corresponded to the initiation of treatment. Following completion of the baseline interview, survivors were randomized to either the intervention or standard care arm based on a minimization algorithm designed to balance arms by recruitment location, site of cancer, oral agent regimen complexity (continuous vs. intermittent dosing), concurrent intravenous chemotherapy, and level of depressive symptoms. Participants in both arms continued to receive standard care, which included scheduled visits to the oncology clinic to

monitor the disease, assess for side effects and dose limiting toxicities, and to adjust dosing. Subsequent interview data were collected via telephone at week four (trial midpoint), week eight (trial endpoint), and week 12 (follow-up). Interviewers were blinded to trial arm assignment. Data from 117 participants who completed any two consecutive interviews were used for this secondary analysis.

Measures

Sociodemographic measures and comorbidity were obtained during the baseline interview. Data on primary site of cancer, whether cancer was metastatic, and oral agent drug category were obtained from the medical records. Oral agents were classified as cytotoxic agents, kinase inhibitors, sex hormone inhibitors (prostate cancer), and other. Survivors who were on more than one drug from the list were on agents from the same category. Number of comorbid conditions treated with medications was determined based on medical records. A total of 25 conditions were considered, including cardiovascular disease, peptic ulcer/gastrointestinal reflux, diabetes, psychological disorders, thyroid disorders, arthritis, based on the primary indications for the medications' use.

Other measures listed below were collected at intake, four, eight, and 12 week telephone interviews:

1) The symptom inventory developed in past work was modified to include symptoms commonly experienced during oral agent treatment. [27] Eighteen symptoms: pain, fatigue, sleep disturbance, anxiety, weakness, headaches, skin rash or sores, numbness or tingling, redness or peeling in hands or feet, swelling of hands or feet, joint pain, mouth sores, lack of appetite, nausea or vomiting, diarrhea, constipation, cough, and shortness of breath were assessed weekly and at each interview for their presence and severity. Survivors were asked if they had experienced each symptom in the past seven days and, if yes, asked to rate the severity of the symptom and how much the symptom interfered with activities of daily life on a scale from one to nine. Symptom severity and symptom interference were summed across the array of symptoms into two indices that could potentially range from zero to 162. Because the array of symptoms is not a collection of items in a scale, the internal consistency reliability was not applicable.
2) Depressive symptoms were assessed via the Center for Epidemiologic Studies Depression (CES-D) 20-item scale.[28] Each item is rated on a 0−3 scale, and the total score can potentially range from 0 to 60. Cronbach's alpha at baseline exceeded 0.90 in this sample.
3) Physical function was assessed using PROMIS 10-item short form.[29] The t-scores have mean 50 and standard deviation 10 in the general United States population.

Data on health services use in the past four weeks were obtained via self-report during four, eight, and 12 week interviews. Participants were asked if they used each type of service (hospital, emergency room, urgent care).

Statistical Analyses

The distributions of types of health services uses and potential predictors were summarized. Use of ED and urgent care were combined based on low counts of separate uses. Longitudinal data were lagged to predict health services use in the four weeks following each PRO assessment using symptoms, physical function, and fixed predictors (age, sex, comorbidity) selected based on past research. Hospitalizations and ED/urgent care uses were analyzed separately using generalized linear mixed effects models with binomial errors for yes/no to each health service use in each four-week period: intake to week four, week four to week eight, and week eight to week 12. Time period (three levels) was included as a class variable to model potentially non-linear patterns. For each health services use outcome, we first fit the models with predictors of age, sex, and number of comorbid conditions. Then we added PRO measure (one at a time) of symptom severity index, symptom interference index, the CESD score, the physical function score to gauge the extent to which each PRO measure improved the prediction of subsequent health services use over and above age, sex, and comorbidity. The importance of PROs was gauged using statistical significance of predictors over time. In addition, areas under the receiver operating characteristic (ROC) curve were evaluated for models without and with PROs. All analyses were performed using SAS 9.4.

The sample size for this post-hoc exploratory analysis was based on the parent trial, and sensitivity power analysis was performed using G*Power 3.1.9.7[30] given the observed service use rates.

Results

Out of 135 survivors randomized to control arm after intake interview, 117 completed two consecutive interviews and were included in this analysis. The distributions of the characteristics of those analyzed were not different from those for the entire control group. Analyzed participants were on average 62 years old with three comorbid conditions treated with medications (Table 1). The median time since diagnosis of cancer being treated with oral agent was 25 months

Table 1
Descriptive Statistics for the Analysis Sample at Baseline (N = 117)

Characteristic	N (%)
Sex	
Male	62 (53%)
Female	55 (47%)
Race	
African American	8 (7%)
Caucasian	106 (91%)
Other/unknown	3 (2%)
Ethnicity	
Hispanic or Latino	3 (3%)
Not Hispanic or Latino	114 (97%)
Level of education	
High school or less	33 (28%)
Some college or completed college	62 (53%)
Graduate or professional degree	22 (19%)
Oral agent category	
Cytotoxic agents	37 (32%)
Kinase inhibitors	56 (47%)
Sex hormone inhibitors	11 (9%)
Other	13 (11%)
Site of cancer	
Breast	27 (23%)
Colorectal	15 (13%)
GI	8 (7%)
Leukemia	6 (5%)
Liver	4 (3%)
Lung	4 (3%)
Lymphoma	1 (1%)
Melanoma	2 (1.7%)
Myeloma	4 (3%)
Pancreatic	13 (11%)
Prostate	13 (11%)
Renal	8 (7%)
Sarcoma	8 (7%)
Brain	1 (1%)
Esophageal	1 (1%)
Other	2 (1.7%)
Metastasis	
Yes	94 (80%)
No	23 (20%)
	Mean (StDev)
Age	62.68 (10.85)
Number of comorbid conditions treated with medications	3.20 (1.83)

Note: StDev = standard deviation.

Table 2
Descriptive Statistics for Health Services use and PROs for Each Time Period

	N (%)
Hospitalization baseline to week 4	
Yes	12 (11%)
No	100 (89%)
Hospitalization week 4 to week 8	
Yes	12 (11%)
No	93 (89%)
Hospitalization week 8 to week 12	
Yes	14 (13%)
No	93 (87%)
ED/urgent care visit baseline to week 4	
Yes	15 (13%)
No	97 (87%)
ED/urgent care visit week 4 to week 8	
Yes	12 (11%)
No	93 (89%)
ED/urgent care visit week 8 to week 12	
Yes	7 (7%)
No	100 (93%)
	Mean (StDev)
Symptom severity at intake	22.82 (20.21)
Symptom severity at week 4	22.42 (20.32)
Symptom severity at week 8	19.46 (16.24)
Symptom interference at intake	17.23 (17.39)
Symptom interference at week 4	17.31 (19.79)
Symptom interference at week 8	14.71 (14.36)
CESD at intake	9.65 (8.64)
CESD at week 4	7.61 (8.15)
CESD at week 8	7.45 (7.05)
Physical function at intake	45.52 (7.62)
Physical function at week 4	45.01 (8.03)
Physical function at week 8	45.76 (8.49)

Note: StDev = standard deviation; CESD = Center for Epidemiologic Studies – Depression; ED = emergency department

(interquartile range from 4 to 88 months). Most prevalent medications for comorbid conditions were for cardiovascular disease (83%), peptic ulcer/gastrointestinal reflux (38%), psychological issues such as depression, anxiety, sleep (37%), hyperlipidemia (27%), and diabetes (20%).

Of 117 survivors analyzed, 112 completed week four, 105 completed week eight, and 107 completed week 12. Summary of their unscheduled health services use and symptom outcomes is in Table 2. The rates of hospitalizations for each four-week period ranged between 11% and 13%, and rates of ED/urgent care visits ranged from 7% to 13%. Given the observed range in rates of health services use from 7% to 13% across time periods, the detectable differences in mean PROs according to service use with power of .80 or greater in two-sided tests at .05 level of significance corresponded to effect sizes (Cohen's d) from 0.78 to 0.98.

In longitudinal models, symptom severity index and physical function score, but not symptom interference or the CESD score were significant predictors of hospitalizations in the next 4 weeks over and above age, sex, and number of comorbid conditions (Table 3). Controlling for PROs, age, sex, and comorbidity were not significant predictors of unscheduled health services use in multivariable longitudinal models. None of the PROs were significant predictors of the ED/urgent care visits over and above age, sex, and comorbidity.

In prediction of health services use, age, sex, and comorbidity alone did not achieve areas above .70, with the exception of the ED/urgent care visits at week eight (Table 3). The addition of symptom severity and physical function increased the areas under the ROC curve to be above .70 with the exception of ED/urgent care visits at week four, which corresponds to the beginning of a new oral agent treatment.

Discussion

The fact that none of the predictors (age, sex, comorbidity, PRO) were significant in relation to ED/

Table 3

Odds Ratios of Unscheduled Health Services use for Unit of Patient-Reported Outcome at a Previous Time Point, Over and above to Age, Sex, and Comorbidity

Outcome	Hospitalizations					ED/urgent Care Visits				
	OR (95% CI) for Unit of PRO at the Previous Time Point	P	Area Under ROC Curve			OR (95% CI) for Unit of PRO at the Previous Time Point	P	Area under ROC Curve		
			Week	Without PRO	With PRO			Week	Without PRO	With PRO
Symptom severity	1.02 (1.001, 1.046)	.04	4	.63	.71	1.01 (0.989, 1.037)	.30	4	.61	.69
			8	.72	.75			8	.73	.76
			12	.68	.72			12	.73	.74
Symptom interference	1.02 (0.997, 1.045)	.08	4	.63	.69	1.01 (0.985, 1.038)	.40	4	.61	.67
			8	.72	.76			8	.73	.76
			12	.68	.67			12	.73	.74
CESD	1.01 (0.954, 1.066)	.76	4	.63	.68	1.01 (0.947, 1.072)	.82	4	.61	.64
			8	.72	.73			8	.73	.77
			12	.68	.68			12	.73	.75
Physical function	0.89 (0.827, 0.958)	<.01	4	.63	.73	0.94 (0.876, 1.014)	.11	4	.61	.70
			8	.72	.81			8	.73	.77
			12	.68	.78			12	.73	.78

Statistically significant effects and areas under the receiver operating characteristic curve ≥.70 are bolded.
ED = emergency department; CESD = Center for Epidemiologic Studies − Depression; OR = odds ratio; CI = confidence interval; PRO = patient reported outcome; ROC = receiver operating characteristic.

urgent care visits suggests that these factors competed for the same share of the variance. This was not the case for hospitalizations, where symptom severity and physical function were significant over and above age, sex, and comorbidity in longitudinal models. Hospitalizations involve more health care resources and have higher cost compared to ED/urgent care uses, and their prediction using symptom severity index or physical index may result in greater cost savings to the health care system. Considering a shorter time period than the next 4 weeks in prediction of ED/urgent care use from PROs may be warranted, particularly because of the temporal nature of symptoms. Capturing symptoms on a more frequent basis may lead to a better prediction of ED/urgent care visits in a shorter subsequent period. Physical function does not change over time as much as symptoms, and it was the strongest PRO predictor of hospitalizations based on the magnitude of the OR and areas under the ROC curve. In addition, in this study hospitalizations were more frequent than ED/urgent care visits, affecting power.

Whereas the addition of any predictor improves the area under ROC curve, the addition of PROs pushed these areas above .70 considered a threshold for good prediction.[31] The addition of symptom interference or the CESD score improved areas under the ROC curve even though these PROs were not statistically significant factors over and above age, sex, and comorbidity. The increases in the area under ROC curve were consistent but relatively small. Clinical significance of these increases warrants further investigation. Of note, the mean CESD scores in this sample were low, and this may explain lack of statistical significance of the CESD as a predictor. In other samples, depressive symptoms were predictive of longer hospital stays among people with advanced cancer.[5]

Limitations of this study include post-hoc exploratory nature of the analysis that was limited by the size of the control group. Only medium to large effect sizes were detectable as statistically significant, which could have resulted in false negative (non-significant) findings. The results of these exploratory analyses should be interpreted as hypothesis-generating for future work. Health services use data were collected using self-report because it would have been impossible to access health records across the multiple cancer centers, hospitals, and payers. Extensive previous research[32-35] documented that self-report was a reliable method to collect health services use data with standardized interview methods and a short recall period. Dates of unscheduled health services use were not available from self-report; it was only known that these events took place in each 4-week period since initiation of the oral agent. In future work, incorporating the time between PRO assessment and event may be considered to determine if ED/urgent care visits may be predicted better from more recent symptoms such as a within a week or two. This would require a more frequent symptom assessment (weekly or even daily) as suggested recently.[19] Weekly symptom assessment data were available in the parent study,[26] but not dates of service uses.

In conclusion, these data support that PROs are "vital signs" [16,17] in that they are clinically relevant predictors for service use outcomes. Yet simply monitoring PROs and providing data to clinicians may not improve symptom outcomes compared to usual care.[36] Actionable decision rules for clinicians in terms when to deploy supportive care services between routinely

scheduled visits are needed. One possibility is to formulate such decision rules based on thresholds in PROs[37] that best predict subsequent use of unscheduled health services. Establishing such thresholds using each PRO and combinations of PROs is a direction for future work.

Disclosures and Acknowledgments

This work was supported by the National Institutes of Health (National Cancer Institute) [grant number 1R01CA162401-01A1]. The authors declare no conflicts of interest

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