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How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/02/Jessica_COI.pdf
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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant Prostate Cancer

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Real-World Patient-Reported Outcomes and Tolerability in MCRPC

Narrative Summary:

Patient-reported tolerability is of increasing importance and regulatory interest in oncology. To date, most of this information derives from trials. However, well-known differences between trial and non-trial populations pose challenges for generalisability. This research aims to evaluate patient-reported tolerability using data from a non-trial registry in prostate cancer. Understanding patient-reported tolerability in non-trial populations in oncology will provide greater insight into how cancer therapies affect patients, which is essential for treatment discussions and decision-making.

Scientific Abstract:

Background: Patient experience, including the ability to tolerate the often severe side effects of therapy, is an important consideration in drug development and clinical care in cancer. However, most patient experience data comes from trials, and differences between trial and non-trial populations limit generalisability. Several new therapies have been approved for the treatment of metastatic castration-resistant prostate cancer (MCRPC), including abiraterone acetate, cabazitaxel, enzalutamide, sipuleucel-T and radium-223. Understanding patient outcomes, including their perception of side effect burden, in non-trial populations is essential for informing treatment decision-making and a more complete understanding of how cancer therapies affect patients. Furthermore, using registry or non-trial data can facilitate the comparison of multiple treatments and provide

greater insight into the patient experience.
Objective: The objectives are to 1) Determine the feasibility of assessing patient-reported tolerability in a real-world registry setting; 2) Assess the level of patient-reported side effect impact, symptoms and quality of life for recently approved prostate cancer therapies using registry data; and 3) Evaluate the measurement characteristics of a single item for patient-reported side effect impact in a non-trial population.
Study Design: This will be a retrospective, secondary analysis using data from a prospective, three-year registry of patients receiving treatment for prostate cancer outside the cancer trial setting.
Participants: Patients with metastatic castration-resistant prostate cancer who did not have previous mCRPC treatment at the time of enrolment, and who received documented treatment with either abiraterone, enzalutamide or docetaxel in the registry (n=1583).
Main Outcome Measures: Primary Outcome: GP5, a single item for overall side effect impact, captured in the FACT-P questionnaire for quality of life in prostate cancer. Secondary outcomes: 1) EQ-5D VAS, a measure of health status captured in the EQ-5D questionnaire; 2) Fatigue (GP1), captured in the FACT-P questionnaire; 3) Pain, captured in the FACT-P and EQ-5D questionnaires; 4) FACT-P total score; 5) FACT-P subscale scores; 6) Medical research utilisation, as captured by the registry.
Statistical Analysis: Aim 1: Descriptive statistics will be used, with completion rates calculated as the number of patients with the GP5 item completed, divided by the number of patients in the target population. Completion rates for neighbouring items (GP4, GP6) and items on other included measures will also be calculated, to provide context for the completion rates for GP5. Aim 2: Regression models and propensity scores will be used to compare the level of side effect impact, symptoms and quality of life across the three treatment types. Aim 3: Correlation and regression models will be used to evaluate the measurement properties of GP5, including the item's association with other patient-reported outcomes (e.g., pain, fatigue, health status) as well as with more objective outcomes (e.g., medical resource utilisation).

Brief Project Background and Statement of Project Significance:

Background: Patient-reported outcomes (PROs) play an increasingly important role in oncology, from medical product development [1] to clinical care [2]. Treatments for cancer often have substantial toxicities and thus tolerability is an important consideration. Although clinician reporting of adverse events will remain essential for the evaluation of safety, regulators such as the Food and Drug Administration (FDA) are also interested in tolerability, which can be measured through patient reporting of symptomatic side effects as well as an overall measure of side effect impact [3]. Summarising tolerability, for example through overall measures of side effect impact, can be helpful in communicating with stakeholders including patients, regulators, and clinicians and potentially in informing treatment decision-making. Thus, there is interest in a summary measure that can help demonstrate how a therapy makes a patient feel [4]. One such item is the Functional Assessment of Chronic Illness Therapy (FACIT) item 5, "I am bothered by the side effects of treatment." GP5 is included in many FACIT instruments.
To date, most information on patient-reported tolerability arises from trial data. Although such data are invaluable for determining product safety and efficacy, studies in multiple myeloma [5] and renal cell carcinoma [6], among others, highlight that many patients with cancer would not be trial-eligible. In particular, patients with comorbidities are less likely to be included in trials [7], and there is a clear need for better data on how cancer therapies affect patients with comorbidities [8]. Registry collection of PRO data in oncology does occur [9], and represents a source of non-trial information about the patient experience.
Significance: Although trial data remain essential for the evaluation of new therapies, additional analyses outside of the trial setting are critical for understanding how new, often costly, therapies affect patients. As most patient experience data about new therapies derive from trials, such analyses address an unmet need in patient-centred research in oncology and can provide essential information about the tolerability of new therapies. As there have been several recent approvals of new therapies for prostate cancer, one of the most common cancers in men, the work is highly relevant for patients, oncologists, and regulators. In addition to providing information salient to communication and treatment decision-making, it helps advance PRO research by providing further information about the measurement characteristics of an item in a widely used questionnaire.

Specific Aims of the Project:

The specific aims of this project are to:
1) Determine the feasibility of assessing patient-reported tolerability in a real-world registry setting;
2) Assess the level of patient-reported side effect impact, symptoms and quality of life for recently approved prostate cancer therapies using registry data;
3) Evaluate the measurement characteristics of a single item for patient-reported side effect impact in a non-trial population.

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Other: Research on an item that can be used as part of patient reporting of side effects in medical product development and product evaluation.

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Data Source: Data will be drawn from NCT02236637, a three-year prospective registry of patients with metastatic castration-resistant prostate cancer (mCRPC) receiving routine medical care. Patients were enrolled any time after diagnosis. The registry enrolled 3003 patients, who were treated with abiraterone acetate + steroid (prednisone or prednisolone), enzalutamide, docetaxel, other chemotherapy regimens, or radium-223 [10]. All therapies in the registry have received FDA approval. Secondary outcomes were collected at baseline (registry enrolment), treatment initiation, and every three months until the end of data collection. Outcome measures included medical resource utilisation, the EQ-5D, and the FACT-P, which contains the GP5 item for side effect bother.
Inclusion/Exclusion Criteria: Patients who have not received previous mCRPC therapy at the time of enrolment and who received any of docetaxel, enzalutamide or abiraterone will be eligible (n=1583, per Chowdhury et al [10]). supplementary analysis.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Aim 1: The primary outcome is the GP5 item on the FACT-P, which asks patients to respond to the statement “I am bothered by the side effects of treatment” (Not at all – Very much/0 – 4). This will be treated as a continuous variable for the primary analyses. For secondary analyses, it will be dichotomised into severe (scores of 3 – 4) vs low (scores <3) bother [11], as well as moderate (scores of 2 – 4) vs low (scores <2) bother.
Aim 2: The primary outcome is the GP5 item. Secondary outcomes: 1) EQ-5D VAS, a measure of health status captured in the EQ-5D questionnaire; 2) Fatigue (GP1), captured in the FACT-P questionnaire; 3) Pain, captured in the FACT-P and EQ-5D questionnaires; 4) FACT-P total score; 5) FACT-P subscale scores; 6) Medical research utilisation, as captured by the registry.
Aim 3: The primary outcome is the GP5 item.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Aim 1: The primary independent variable is treatment type. This will be treated as a categorical

variable.
Aim 2: We will adjust for important clinical and sociodemographic factors collected in the registry and used as covariates in prior analyses [10], including age, region, ECOG performance status, Gleason score, M stage, time from diagnosis, presence of metastases (bone/visceral), and presence of comorbidities. Following Chowdhury [10], age and time from diagnosis will be treated as continuous variables and the remainder will be treated as categorical.
Aim 3: The primary independent variables are 1) the quality of life visual analogue scale from the EQ-5D, treated as a continuous variable; 2) medical resource utilisation (total hospitalisation days, total ED visits, total outpatient visits), treated as a continuous variable; 3) reason for treatment cessation, treated as a categorical variable; and 4) well-being and quality of life domains in the FACT-P, treated as continuous variables. If available, information on reasons for medical resource utilisation will be an independent variable, treated categorically. Each variable will be analysed separately.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Aim 1: We will examine completion rates by region and presence of comorbidities. If there is sufficient data to allow us to model completion rates statistically, we will adjust for important clinical and sociodemographic factors collected in the registry and used as covariates in prior analyses [10], such as age, region, ECOG performance status, Gleason score, M stage, time from diagnosis, presence of metastases (bone/visceral), and presence of comorbidities. Following Chowdhury [10], age and time from diagnosis will be treated as continuous variables and the remainder will be treated as categorical.
Aim 2: Other variables that are relevant to generate the propensity scores will be used in the analysis. This will be determined with the clinical investigator on the team.
Aim 3: None.

Statistical Analysis Plan:

Aim 1: The initial analyses will be descriptive in nature. For baseline and three months, we will produce descriptive statistics of the relevant variables. For GP5, we will examine completion rates at each time point. If feasible, a logistic regression model will be used to examine the association of patient clinical and sociodemographic factors with completion of GP5 at enrolment. Univariable analyses will be used to assess the suitability of variables for inclusion in the final model. Variables shown to be significant in univariable analyses (p<0.25) will be included in a multivariable logistic regression model.
Aim 2: We will compare the mean GP5 score at treatment initiation and at three months after treatment using linear regression models, or proportional odds models if linear regression models are not suitable due to assumption violations. Similarly, we will compare the percentage of patients reporting moderate or severe side effect bother on the dichotomized GP5 at each of these timepoints using logistic regression. Changes in score from baseline to three months will be calculated, and trajectories visualized. Score changes accounting for difference in patient characteristics will be evaluated using regression models.
Propensity score adjustment will be used to achieve comparability of patient populations, as the data are observational and treatment choices not assigned randomly. The primary analysis will be between the two newer therapies, enzalutamide and abiraterone. Propensity scores will be generated using logistic regression models. Standardised differences of 99th percentile given the value of the 99th percentile, weights <1st percentile given the value of the 1st percentile). Following the estimation of weights, they will be included in the regression models, with robust standard errors used to account for the error introduced by weighting. As an additional analysis, we will employ propensity score approaches for multiple treatments, which are relatively new in the statistical literature and will enable us to compare tolerability as measured by GP5, symptoms and quality of life between enzalutamide, docetaxel and abiraterone.
Aim 3: We will evaluate the association between GP5 and the independent variables using Pearson’s r and Spearman’s rho, as appropriate for the different variables. Correlations of ≥0.40 will be a priori considered meaningful.
Missing Data Handling: The extent of missing outcome and covariate data will be evaluated as part

of the descriptive analysis in Aim 1. Missingness patterns will be examined and multiple imputation (MI) will be used to address missing data. For Aim 2, following previous approaches, the propensity scores will be estimated and analyses conducted within each imputed dataset, and then pooled at the end using standard combining rules for multiply imputed data [12]. For Aim 3, if suitable, correlation analyses will be conducted within multiply imputed datasets.
Supplementary Analysis: T-tests or chi-square tests, as appropriate for the different variables, will be used to compare the clinical and sociodemographic characteristics of the included and excluded patient populations.

Software Used:

STATA

Project Timeline:

The project can start when the data are available. Estimated start: May 2024.
Data Cleaning/Preparation: 3 months (May 2024 – July 2024)
Data Analysis: 4 months (August 2024 – December 2024)
Manuscript Writing and Revisions: 8 months (January 2025 – August 2025) (this includes anticipated journal submission and revision time)
Project Closeout: September 2025

Dissemination Plan:

We aim to produce two manuscripts. One manuscript will focus on the cross-treatment comparison and will be aimed at a more clinical audience. This will be submitted to a clinical cancer journal such as Journal of Clinical Oncology or JAMA Oncology. The focus of the second manuscript will be on the feasibility of the GP5 tolerability item in a registry setting and its measurement characteristics, and will be submitted to a methodological/field journal such as Journal of Patient-Reported Outcomes or Quality of Life Research.
In addition, we will aim to disseminate the findings through presentations at conferences, such as the Clinical Oncology Society of Australia, American Society of Clinical Oncology or the International Society for Quality of Life Research.

Bibliography:

1. Kluetz PG, Slagle A, Papadopoulos EJ, et al. Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms. *Clin Cancer Res* 2016; 22: 1553-1558. 2016/01/14. DOI: 10.1158/1078-0432.CCR-15-2035.
2. Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *JAMA* 2017; 318: 197-198. 2017/06/07. DOI: 10.1001/jama.2017.7156.
3. Kluetz PG, Kanapuru B, Lemery S, et al. Informing the Tolerability of Cancer Treatments Using Patient-Reported Outcome Measures: Summary of an FDA and Critical Path Institute Workshop. *Value Health* 2018; 21: 742-747. 2018/06/19. DOI: 10.1016/j.jval.2017.09.009.
4. Basch E. Toward patient-centered drug development in oncology. *N Engl J Med* 2013; 369: 397-400. 2013/07/05. DOI: 10.1056/NEJMp1114649.
5. Shah JJ, Abonour R, Gasparetto C, et al. Analysis of Common Eligibility Criteria of Randomized Controlled Trials in Newly Diagnosed Multiple Myeloma Patients and Extrapolating Outcomes. *Clin Lymphoma Myeloma Leuk* 2017; 17: 575-583 e572. 2017/09/10. DOI: 10.1016/j.clml.2017.06.013.
6. Mitchell AP, Harrison MR, George DJ, et al. Clinical trial subjects compared to “real world” patients: Generalizability of renal cell carcinoma trials. *J Clin Oncol* 2014; 32: 6510.
7. Unger JM, Hershman DL, Fleury ME, et al. Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation. *JAMA Oncol* 2019; 5: 326-333. 2019/01/11. DOI: 10.1001/jamaoncol.2018.5953.
8. Sarfati D, Koczwara B and Jackson C. The impact of comorbidity on cancer and its treatment.

CA Cancer J Clin 2016; 66: 337-350. 2016/02/19. DOI: 10.3322/caac.21342.
9. Sztankay M, Neppl L, Wintner LM, et al. Complementing clinical cancer registry data with patient reported outcomes: A feasibility study on routine electronic patient-reported outcome assessment for the Austrian Myelome Registry. *Eur J Cancer Care (Engl)* 2019; 28: e13154. 2019/08/30. DOI: 10.1111/ecc.13154.
10. Chowdhury S, Bjartell A, Lumen N, et al. Real-World Outcomes in First-Line Treatment of Metastatic Castration-Resistant Prostate Cancer: The Prostate Cancer Registry. *Target Oncol* 2020; 15: 301-315. 2020/06/06. DOI: 10.1007/s11523-020-00720-2.
11. Pearman TP, Beaumont JL, Mroczek D, et al. Validity and usefulness of a single-item measure of patient-reported bother from side effects of cancer therapy. *Cancer* 2018; 124: 991-997. 2017/11/14. DOI: 10.1002/cncr.31133.
12. Roydhouse JK, Gutman R, Keating NL, et al. Propensity scores for proxy reports of care experience and quality: are they useful? *Health Serv Outcomes Res Methodol* 2020; 20: 40-59.