



Review Article

Review of Stakeholder Preferences for Non-Metastatic Castration-Resistant Prostate Cancer Treatments

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Abstract

The goals of treating non-metastatic castration-resistant prostate cancer (nmCRPC) patients are to delay metastasis and prolong life, while maintaining the quality of patients' survival. The recent approval of second-generation androgen-receptor inhibitors (SGARIs) in the United States has expanded the treatment landscape for nmCRPC. Large-scale randomized controlled trials showed that SGARI treatment options have similar efficacy, but different safety profiles. Two recent discrete choice experiment (DCE) studies conducted in the United States, evaluated the benefit-risk tradeoffs of patients, caregivers and physicians

for nmCRPC treatments. The aim of this review is to summarize these two studies and highlight differences in the preferences among these three stakeholder groups with respect to adverse events (AEs) of specific interest in nmCRPC. Both DCE studies included 5 AE attributes: frequency or level of severity of fatigue, skin rash, cognitive impairment, risk of serious fracture, risk of serious fall. Survey results from patients (n=143), caregivers (n=149), and physicians (n=74 oncologists, n=75 urologists) were analyzed using random parameters logit models generating preference weights for each attribute level. AE reduction was more important than improving OS

for physicians and even more prominently for patients and caregivers. As government healthcare agencies, globally, continue integrating patient feedback and evidence into their decision-making processes, the role of preference methodology in generating such evidence, may be expected to grow.

Keywords: Prostate cancer; Preferences; Stakeholders; Decision-making; Benefit-risk

1. Introduction

Prostate cancer is the third most common cancer in the United States [1]. The American Cancer Society estimates about 191,930 new cases of prostate cancer will be diagnosed in the US in 2020 and about 33,330 men are projected to die from prostate cancer [1]. Non-metastatic castration-resistant prostate cancer (nmCRPC) is a stage of the disease during which the cancer becomes resistant to hormonal therapy, but has not yet spread to other areas of the body [2]. The goal of treating nmCRPC patients is to delay metastasis and prolong life while maintaining the quality of patients' survival [3, 4]. The recent approval of second-generation androgen-receptor inhibitors (SGARIs) in the United States has expanded the treatment landscape for nmCRPC [5]. Trials showed that SGARI treatment options have similar efficacy, but different safety profiles [5]. Two recent preference studies conducted in the United States evaluated the benefit-risk tradeoffs of patients, caregivers and physicians for nmCRPC treatments [6, 7]. This review summarizes these two studies and highlights differences in the preferences among these three stakeholder groups. Understanding differences in preferences among patients, caregivers, and physicians will

enhance shared decision-making between physicians and patients/caregivers, and better inform health technology assessment (HTA).

2. Materials and Methods

2.1 Study design and sample

The study design in both Srinivas et al. publications utilized discrete choice experiments (DCEs). In a DCE respondents were presented hypothetical scenarios regarding medication profiles and corresponding outcomes to elicit their preferences for treatment attributes and their willingness to tradeoff benefits and risks [6, 7].

2.2 Survey development

Based on feedback from initial interviews and discussion with clinical experts, both DCE studies focused on two efficacy attributes: overall survival (OS) and time to pain progression (TPP); and 5 adverse event (AE) attributes: frequency or level of severity of fatigue, skin rash, cognitive impairment, risk of serious fracture, risk of serious fall. Researchers ensured that respondents understood the definitions of the attributes and levels before answering the questions [6, 7]. The two studies initially included the same attributes and levels. However, severe levels for fatigue, skin rash, and cognitive impairment (Table 1) were excluded for patients and caregivers, because they were unwilling to accept these severe levels of AEs, regardless of the possible OS benefit [7]. Due to this difference in the severity levels of AE attributes between the two studies, the choice sets are not the same, and therefore we cannot directly compare the results in a statistical manner [6, 7].

Attribute	Physician DCE Levels	Patient/Caregiver DCE Levels
Overall survival	4 years and an additional 12 months 4 years and an additional 6 months 4 years and an additional 3 months	
Time to pain progression	3 years and an additional 12 months 3 years and an additional 6 months 3 years and an additional 3 months	
Fatigue	None Mild-to-moderate Severe	None Mild Moderate
Skin rash	None Mild-to-moderate Severe	None Mild Moderate
Cognitive impairment	None Mild-to-moderate Severe	None Mild Moderate
Risk of serious fall	None 5% 8%	
Risk of serious fracture	None 5% 8%	

Table 1: Attributes and Levels in the Two DCE Studies.

2.3 Sample selection

2.3.1 Inclusion criteria: The patients and caregivers were self-screened online from February to April 2019. Patients had to be at least 18 years old, diagnosed with prostate cancer, have rising PSA levels, and not been told their cancer had spread to any other part of his body. Of the 150 patients screened, 143 were included in the final analysis. Each caregiver was required to be the primary caregiver of

a patient who met the inclusion criteria. Of the 150 caretakers screened, 149 were included in the final analysis [7]. The physicians (n=150 oncologists, n=150 urologists) were participants in existing online panels and screened in January 2019. Physicians were required to have experience treating nmCRPC patients, be a urologist or oncologist in the US, and at least 18 years of age. Of the 300 physicians screened, 149 physicians (n=74 oncologists, n=75

urologists) were included in the final analysis [6]. For all stakeholder groups, respondents were excluded if consent was not provided or if they had participated in a similar survey in the past six weeks [6, 7]. The survey results were analyzed using random parameters logit models for both studies generating preference weights for each attribute level. Furthermore, relative attribute importance scores were calculated for each attribute. Both study protocols were approved by centralized US Institutional Review Boards [6, 7].

3. Results

3.1 Respondent characteristics

For the patients included in the sample, the mean age was 53.04 years old (SD: 14.2) and the men were mostly white (84.6%), had a college degree or higher (83.9%), married (72.7%), and employed full-time (60.1%) [7]. The caregivers had mean age of 46.3 years (SD: 11.9) with some caring for a parent with nmCRPC (47.7%), and most were white (77.9%), and employed full-time (73.2%) [7]. The physicians had mean age of 51.3 years (SD: 10.7), were mostly white (67.1%), with a mean of 17.9 years in clinical practice (SD: 8.5) [6].

3.2 Relative importance of attributes

In both studies, all three stakeholder groups favored a 9-month improvement in OS over a comparable improvement in TPP. Patients with nmCRPC valued reducing each of the

AEs more than on a 9-month improvement in OS across the levels assessed in the DCE [7]. Caregivers valued reducing serious fractures, serious falls, and cognitive impairment more than a 9-month improvement in OS [7]. Physicians valued a reduction in cognitive impairment and risk of serious fracture more than a 9-month increase in OS [6]. Table 2 shows the relative importance of all the treatment attributes for the various stakeholders. In summary, AE reduction was more important than improving OS for physicians and even more prominently for patients and caregivers.

3.3 Quantitative benefit-risk assessment

The DCEs estimated how much OS the stakeholders were willing to trade off to mitigate an AE. For example, patients were willing to trade off almost 7 months of OS to reduce risk of a serious fall from 5% to none. For the same risk reduction in serious fall, caregivers were willing to give up even longer OS; i.e., 9 months [7]. In contrast, physicians were willing to trade off just 2 months of OS to spare the patient the same 5% risk reduction in serious falls [6]. This finding was expected as the patients and caregivers valued this attribute more highly than did physicians (Table 2) [6, 7]. Due to the difference in the severity levels of fatigue, skin rash, and cognitive impairment between the two studies, the choice sets are not the same; hence, we cannot directly compare the results in a statistical manner [6, 7].

Physicians	Patients	Caregivers
Cognitive impairment	Risk of severe fracture	Risk of severe fracture
Risk of severe fracture	Risk of severe fall	Risk of severe fall
Overall survival	Cognitive impairment	Cognitive impairment
Fatigue	Fatigue	Overall survival
Risk of severe fall	Rash	Fatigue
Rash	Overall survival	Rash
Time to pain progression	Time to pain progression	Time to pain progression

*Note: The two studies cannot be directly compared because the attributes and levels are not the same as shown in Table 1.

Table 2: Relative Importance of the Treatment Attributes in the Two DCE Studies*.

4. Discussion

Since nmCRPC is generally asymptomatic, ensuring patients receive treatment that prolong life without compromising their daily activities is crucial [3, 4, 6, 7]. Risk of AEs is an important consideration in nmCRPC, due to its association with increased risk for therapy discontinuation [3]. Physician input typically influences the treatment decisions made by patients and must strike a delicate balance between safety and efficacy, and the patients’ individual preferences, as most men with prostate cancer desire to be involved in the decisions related to their treatment [3, 8].

Although prolonging life is important to nmCRPC patients their caregivers, and treating physicians alike, they may place different values on avoiding certain AEs. Table 2 shows that for patients, caregivers and physicians cognitive impairment and severe fractures were in their respective top 3 attributes and were considered more important than survival. This is a telling insight, as generally in cancer, survival is a key treatment goal for all three groups alike.

Despite this similarity, physicians placed OS as third most important, whereas patients and caregivers deemed cognitive impairment (third) as more important than OS (fourth). This discrepancy between physicians and patients and caregivers is not unique to nmCRPC. A patient and physician preference study that investigated the differences in the risk tolerance between efficacy and AEs in the type-2 diabetes population similarly found that physicians placed more emphasis on efficacy outcomes, while patients were more concerned with quality of life [9].

In 2016, the Food and Drug Administration (FDA) launched patient engagement efforts to elicit feedback from patients and caregivers on drugs, biologics, and medical devices for consideration when making recommendations for approvals [10]. European HTAs and consortia such as the ISPOR task force and PREFER focus group are increasingly interested in preference study best practices and the role of resulting evidence, especially of DCE, within value assessment [11]. IQWiG (Institute for Quality and Efficiency in Health Care) in Germany has recognized

and incorporated DCE as a measure of overall benefit within the organization's "General Methods" since Version 5.0 in 2017 based on earlier pilot studies [12]. More recently, NICE (National Institute for Health and Care Excellence) in the UK has acknowledged DCE as an evidence stream for HTA [11].

As HTAs continue to adopt and support additional patient preference-based initiatives and partnerships to integrate patient input into decision-making, we expect a greater emphasis on patient preferences informing healthcare decisions on a broader scale and a paradigm shift in the treatment-decision dialogues between patients, caregivers, and physicians [6, 7, 13, 14, 15].

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Disclosure

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