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Original Article

Assessing recent trends of oncologists in the treatment of patients with prostate cancer

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Abstract

The available options for treating prostate cancer (PC) have increased dramatically in recent years with new chemical, hormonal, and immunological treatment receiving Food and Drug Administration approval since 2008. We conducted a longitudinal study among a cohort of 150 US oncologists to identify how they treat patients with PC, and how these new treatment options are impacting management. From the results of a case vignette survey disseminated to this cohort in 2011, 2012, and 2013; we observed dramatic shifts in treatment choices for a patient with asymptomatic and symptomatic metastatic castration-resistant prostate cancer and identified a lack of familiarity with newer immunotherapies for PC. With the increased number of options available including immunotherapies, comes a concomitant increase in the complexity of treatment regimens. Given this level of complexity, it is imperative for cancer educators to effectively keep oncologists abreast of the latest evidence-based management.

Keywords: Immunotherapy, practice patterns, prostate cancer

INTRODUCTION

An estimated 23,300 men will be diagnosed with prostate cancer (PC), and 29,480 will die of the disease in the United States in 2014.[1] Accounting for 27% of new cancer diagnoses and 10% of cancer deaths, PC continues to be the most common malignancy and the second most common cause of cancer death among men in the US. The lifetime probability of developing PC is 15.3% (1 in 7) for American males. In addition, up to 20% of patients with PC develop castration-resistant prostate cancer (CRPC) disease within 5-year of follow-up and 84% of those CRPC diagnoses also included metastatic PC.[2] Encouragingly, the 5-year survival rate from diagnosis has increased substantially over the past generation, from 66% in 1975 to 100% in 2013.[3] The improvement in survival noted in the past four decades has been primarily attributable to increased public awareness that has led to earlier detection and to the development of more effective therapies.[1,3]

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The landscape for treating CRPC is evolving rapidly, with five agents approved for metastatic disease since 2010.[4,5] Moreover, these agents encompass a wide array of treatment approaches including chemotherapy (cabazitaxel), hormonal (abiraterone, enzalutamide), radiotherapy (radium 223), and immunotherapy (sipuleucel-T).[6] With the wide armamentarium now available to the oncologist to strategize the treatment plan, developing an optimum regimen in an optimum sequence has become even more complex. It has also become even more important to understand

how oncologists are incorporating these newer agents into treatment regimens and the evidence on which they are basing their treatment decisions.

METHODS

The practice patterns of US-practicing oncologists in managing patients with PC were quantified and assessed using a survey instrument with up to 33 questions. Clinical vignette surveys have been validated as cost-effective tools in measuring clinical practice quality.[7,8] Vignettes are now commonly used in many settings around the world as a validated way to make quality comparisons.[9,10] Recently, vignettes have been used with US community-based rheumatologists to assess the quality of practice and variation in care; and in the Philippines over a 3-year period in a randomized controlled trial to assess the impact of a pay for performance program on pediatric health outcomes.[11-13]

The survey used three clinical case presentations including: (1) A 62-year-old man with Gleason's 4 + 4 adenocarcinoma at initial diagnosis that eventually becomes castration-resistant, (2) a 77-year-old man with asymptomatic CRPC and progressive bone metastases, and (3) a 59-year-old man with symptomatic metastatic castration-resistant prostate cancer (mCRPC) (Gleason 3 + 4 adenocarcinoma of the prostate with multiple pelvis and spine metastases). The survey was initially disseminated to a random national sample of oncologists in February 2011 with 151 oncologists returning completed surveys. The survey was re-distributed in February 2012 and December 2013 to this same cohort of oncologists. Responses totaled as 111 in 2012 and 104 in 2013. In each of the patient case vignettes, respondents made their treatment selection based on the individual clinical presentation. In 2011, these selections were made in an open-ended format allowing respondents to write in their selections. In 2012 and 2013, cued responses were used in a multiple-choice format based on the 2011 open-ended responses with updates to reflect the latest approved treatment options. Confidence in managing patients in each setting was assessed using a 10-point Likert scale format. Respondents' demographic information was also obtained. Additional questions addressing respondents' perceptions, and awareness of immunotherapies for PC were added to the 2013 survey. To obtain the initial study sample, the survey was distributed to a random national sample of oncologists. Participation in the study was limited to US-practicing medical oncologists or hematologic oncologists who see at least 11 patients with PC per month. For the 2012 and 2013 studies, the survey was distributed by E-mail only to the previous 2011 respondents.

RESULTS

Respondent demographics

The sample of oncologists was almost evenly divided between medical oncologists (50.5%) and hematologic oncologists (49.5%). These oncologists managed a mean of 11 patients with metastatic PC per week and on average had graduated from medical school 27-year ago. Almost all were board certified (98%) and the most were in private practice (75.0% group, 11.5% solo).

Early postsurgical management of a patient with high-risk, localized prostate cancer

Respondents were queried on their management approach for a 62-year-old man with Gleason's 4 + 4 adenocarcinoma of the prostate (prostate specific antigen [PSA] of 4.8 ng/mL) who underwent a radical prostatectomy with retroperitoneal lymph node dissection. Margins were clear with no nodal involvement, and his postsurgical nadir PSA was 0.12 ng/mL. His PSA increased to 2.6 ng/mL 6-month after surgery, but he remained asymptomatic. After starting a luteinizing hormone-releasing hormone (LHRH) agonist, his PSA dropped to 0.08 ng/mL, but 8-month later was back up to 6 ng/mL.

For the next step in management of this patient, 81% of respondents in 2013 opted to add bicalutamide to the LHRH agonist, similar to responses obtained in 2012 (87%) and 2011 (78%).

In assessing confidence in managing the patient at this stage, 39% of respondents were "very" confident (8–10 on a 10-point Likert scale) in treating the patient to an optimal outcome, compared to 46% in 2011 and 56% in 2012. Only 5–6% were not confident (1–3 on a 10-point Likert scale) at any of the 3 times points.

In the continuation of the case vignette, bicalutamide was added to the patient's LHRH agonist. After an initial PSA drop to 1.2 ng/mL, it began to rise. Anti-androgen withdrawal did not produce any effect, with his PSA rising to 6.5 ng/mL.

Respondents made their second management decision at this point and had much less consensus compared to their choice of bicalutamide earlier in the presentation [Figure 1]. The most likely choices were: Ketoconazole and hydrocortisone (40%) in 2011; evenly divided between ketoconazole/hydrocortisone (25%) and abiraterone/

prednisone (25%) in 2012; and abiraterone/prednisone (42%) in 2013. A notable portion of respondents opted for sipuleucel-T in each year (10% in 2011, 23% in 2012, and 15% in 2013).

Managing a patient with asymptomatic metastatic castration-resistant prostate cancer

The second vignette was of a 77-year-old patient with mCRPC with a PSA of 128 ng/mL and metastases in the ribs, spine, and pelvis at the initiation of management. After a 2-week course of bicalutamide followed by leuprolide, his PSA dropped to 1.8 ng/mL. He continued leuprolide every 3-month and did well over the following 18-month. At his last 3 quarterly visits, his PSA rose from 2.2 ng/mL to 3.5 ng/mL to 12 ng/mL. He had remained asymptomatic throughout his care, but a new bone scan demonstrated new, small rib lesions.

Confidence in treating this, patient remained very consistent over the 3-year span with 42–47% being "very" confident (8–10 on a 10-point Likert scale) and 49–51% being "somewhat" confident (4–7 on a 10-point Likert scale).

As a next step in management, the most likely selection was bicalutamide at all 3 times points (36% in 2011, 61% in 2012 and 51% in 2013). However, several shifts were observed among the less frequently selected options: Sipuleucel-T use increased from 8% in 2011 to 22% in 2012 and 29% in 2013, denosumab use more than doubled from 12% in 2011 to 27% in 2013, while zoledronic acid use remained relatively constant at 18% (2011), 11% (2012), 14% (2014), and abiraterone use increased from 9% in 2012 to 16% in 2013. Conversely, docetaxel use dropped from 16% in 2011 to 5% in 2012 and 3% in 2013, as did ketoconazole use, from 16% in 2011 to 3% in 2012 and 5% in 2013.

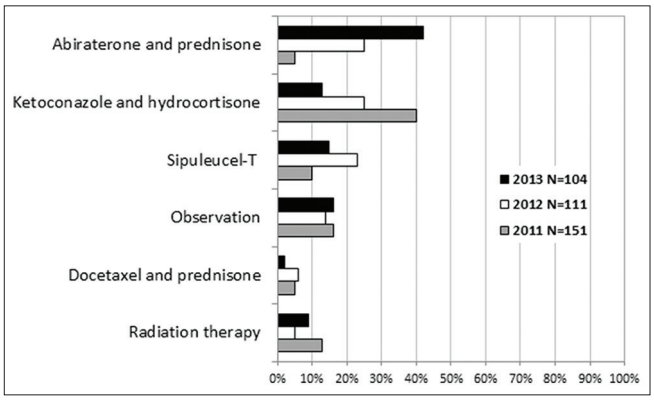

Figure 1: Treatment selection for an asymptomatic 62-year-old patient with localized high-risk prostate cancer following progression after first-line hormonal therapy and no response to anti-androgen withdrawal

In the continuation of the case vignette, the patient was continued on leuprolide and restarted on bicalutamide, which resulted in his PSA dropping to 1.5 ng/mL (previous PSA was 12 ng/mL), but 6-month later his PSA began to rise. At this point, his anti-androgen therapy was withdrawn. Respondents were asked to make a management choice for the patient upon further progression.

Again, several shifts in treatment selections were observed [Figure 2]. Abiraterone use increased from 42% in 2012 to 64% in 2014 while ketoconazole use dropped from 39% in 2011 to 20% in 2012 and 16% in 2013. In 2013, respondents were over twice as likely to select enzalutamide (21%) than docetaxel (10%).

Managing a patient with symptomatic metastatic castration-resistant prostate cancer

The final case vignette was a 59-year-old man with Gleason 3 + 4 adenocarcinoma of the prostate with multiple metastases in the pelvis and spine. His disease became castration-resistant after a 14-month regimen of goserelin, bicalutamide, and zoledronic acid. Subsequent anti-androgen withdrawal was ineffective. Over a 6-month span, although he maintained an Eastern Cooperative Oncology Group performance status of 1, his PSA increased from 8 to 35 ng/mL, he lost 5 pounds and developed right lateral chest pain, and new lesions were detected in his ribs. At this point, respondents were asked which treatment was appropriate for the patient.

Similar to the preceding case vignettes, dramatic shifts in treatment selection were observed [Figure 3]. Abiraterone use increased from 23% in 2012 to 56% in 2013 while docetaxel use decreased from 72% to 29% from 2012 to 2013.

Despite these shifts in treatment, confidence levels in managing this symptomatic patient were almost identical to

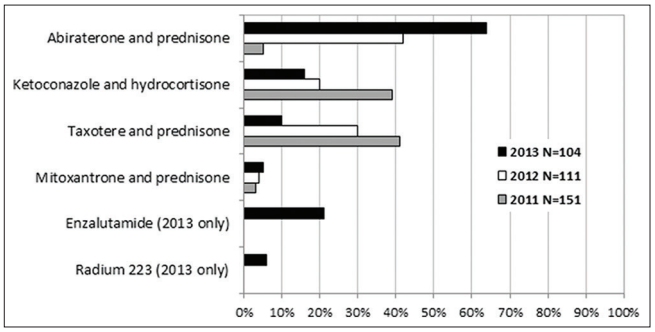

Figure 2: Treatment selection for an asymptomatic 77-year-old patient with metastatic prostate cancer, prostate specific antigen (PSA) dropped from 128 ng/ml to 2.2 ng/ml with initial bicalutamide and long-term luteinizing hormone-releasing hormone therapy for 18-month, but rose back to 12 ng/ml over the next 6 months and new rib lesions are detected. Restarting the bicalutamide dropped his PSA to 1.5 ng/mL but then began rising, and anti-androgen withdrawal showed no effect

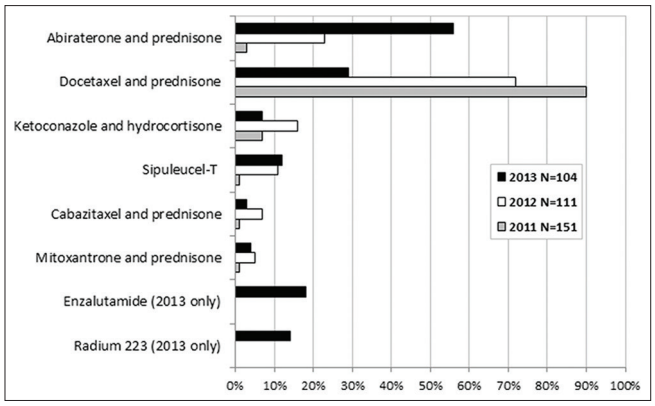

Figure 3: Treatment selection for a 59-year-old patient, in good performance status, with symptomatic metastatic castration-resistant prostate cancer following 14-month of therapy (goserelin, bicalutamide, and zoledronic acid, followed by bicalutamide withdrawal), prostate specific antigen rose over the past 6-month from 8 to 35 ng/ml, bone mets have spread from his pelvis and spine to his rib, and he developed pain in his right lateral chest

levels observed in the previous 2-year, with 42–47% being "very" confident (8–10 on a 10-point Likert scale) and 49–51% being "somewhat" confident (4–7 on a 10-point Likert scale).

Respondents' next choice was to select a treatment for the patient in the setting of progression after receiving docetaxel while maintaining a good performance status. In 2011, 85% of clinicians selected cabazitaxel compared to 31% in 2012 and 27% in 2013. In 2012, abiraterone replaced cabazitaxel as the most frequently selected treatment (69%); but in 2013, respondents were almost split between abiraterone (53%) and enzalutamide (46%) as the most frequently selected treatments. Seventeen percent of respondents included radium 223.

Knowledge and perceptions of immunotherapies for prostate cancer

Less than a third of respondents considered themselves "very" familiar (8–10 on a 10-point Likert scale) with the role of the immune system in cancer pathophysiology (28%) or in cancer immunosurveillance (30%). Most considered themselves "somewhat" familiar (4–7 on a 10-point Likert scale) with each topic (68% with pathophysiology, 64% with immunosurveillance). Respondents considered themselves slightly more familiar with safety and efficacy data of available immunotherapies, with 41% "very" familiar with efficacy data and 34% "very" familiar with safety data.

Respondents rated how important a role they believe immunotherapy will play in improving the outcomes of patients with advanced PC: 31% considered it to be "very" important and 60% considered it as only "somewhat" important.

When asked to select what stage of disease they believe that immunotherapies for PC will be most useful, the most frequent selection was stage IV (73%), with stage IIIA the next most frequent choice (27%); the least frequently selected options were stage IA (15%) and stage IIA (18%).

DISCUSSION

The primary goal of this longitudinal study was to identify the practice patterns of oncologists in the community in their approach to managing patients with PC. In this regard, the cohort of 151 oncologists that participated were very representative of this audience, with the vast majority in private practice and board certified, but very few (8%) practicing in a National Cancer Institute-sponsored center.

In making treatment choices for the different stages of the disease presented in the case vignettes (localized PC, asymptomatic mCRPC, and symptomatic mCRPC), respondents had the most consensus for the primary setting in that at least 78% of respondents, in each of the 3-year studied, added bicalutamide to the patient's LHRH agonist in response to a rising PSA. This treatment choice is in line with current evidence.[14] However, once the patient progressed, the impact of the newer hormonal therapies was very evident with one CYP17a inhibitor, abiraterone, supplanting another CYP17a inhibitor, ketoconazole, as the most frequently selected option.[15] This currently represents an off-label use for abiraterone given that its current indication, although expanded to include the use in the predocetaxel setting, remains only for metastatic disease.[16]

Bicalutamide was also the most frequently selected therapy for the asymptomatic patient with CRPC and metastases in his ribs, spine, and pelvis. This patient had done well over an 18-month span with a regimen of induction bicalutamide and leuprolide with subsequent PSA rise from 2.2 ng/mL to 12 ng/mL over a 6-month span accompanied by new rib lesions. However, with this patient there was less consensus among respondents compared to the patient with localized disease. About half of respondents opted to restart his bicalutamide, while almost a third opted for sipuleucel-T (which is over a 3-fold increase from 2011). Even though the patient's bone metastases continued to progress, only 41% of respondents in 2013 opted to address it with either denosumab or zoledronic acid, which may be a reflection of the patient's asymptomatic state. These data concur with other studies of oncologists and urologists that have documented the underutilization of these agents in patients with bone metastases until a skeletal-related event occurs.[17,18] Once the patient progressed following treatment with bicalutamide and leuprolide then anti-androgen withdrawal, the shift in the last 3-year toward hormonal therapy and away from chemotherapy was dramatic. Abiraterone use increased 50% from 2012 to

2013, and 21% used enzalutamide off-label, while docetaxel use decreased by 75%.

Similar shifts were observed in treatment for the symptomatic patient as well, with over a 2-fold increase in the use of abiraterone from 2012 to 2013 and a 67% decrease in the use of docetaxel since 2011, once the patient progressed after 14-month of therapy (goserelin, bicalutamide, zoledronic acid, followed by bicalutamide withdrawal). Although the patient had developed pain in his right lateral chest and new bone lesions were detected in his ribs but no visceral metastases were present, less than a fifth of the 2013 respondents selected radium 223.

Although the respondents' approach to treatment has changed over the past 3-year, the new treatment options have not increased the level of confidence in treating patients to an optimum outcome. Those that are "somewhat confident" still slightly outnumber those that are "very" confident.

Respondents in 2013 remain not very familiar with safety and efficacy data of available immunotherapies and even less familiar with the role of the immune system in cancer pathophysiology and immunosurveillance. In addition, they maintain an apparent skepticism on how important a role they expect immunotherapies to play in PC therapy, with less than a third believing that role will be "very" important.

The results of this 3-year study clearly demonstrate the shifts in practice patterns that have occurred in how oncologists treat patients with PC since 2011. The results also clearly demonstrate the impact that new hormonal therapies are having in the treatment paradigm. Gaps in evidence-based treatment decisions regarding some of these newer therapies were also demonstrated. With the additional therapeutic options available to treat PC, the added complexities associated with immunotherapies and the lack of familiarity with these agents that currently exists, the task of keeping oncologist up-to-date with the latest evidence are daunting. Additionally, with the number of PC therapies that are currently in late-stage development, that task will continue to be a challenge.[19]

With the dramatic new findings presented at the 2014 ASCO meeting regarding improved survival with combined chemohormonal therapy for newly diagnosed patients with widespread metastatic disease, it is likely that the trend will shift back towards earlier chemotherapy.[20] Keeping clinicians educated on the most favorable sequence of therapies will be very important for optimal patient outcomes.

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