INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Treatment of Prostate Cancer*
-November 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a review of pharmacotherapy for advanced prostate cancer (PC), including gonadotropin-releasing hormone (GnRH) agonists and antagonists, collectively referred to as androgen deprivation therapeutics (ADT); androgen receptor pathway inhibitors (ARPIs); the androgen synthesis inhibitor abiraterone; chemotherapeutic agents (chiefly taxanes); and agents used to treat bony metastases. Following clinical review and analysis, the NPTC voted to **ADD any depot formulation of leuprolide** to the National Core Formulary.

Discussion:

Prostate cancer is the second most commonly diagnosed cancer in the United States overall after female breast cancer, and the 5th leading cause of cancer death. The median age at diagnosis is 67, the 5-year survival rate approximately 97%, and about 1 in 6 men have evidence of metastases at initial diagnosis.[1,2] The incidence of prostate cancer in American Indian/Alaskan Native (AI/AN) men is lower than that of most other ethnic groups, at 70 per 100,000 men compared with 112 per 100,000 overall.[2] Cancer-specific mortality is comparable to that of Caucasian patients, though AI/AN men present at a less favorable Gleason grade and stage of their disease, suggesting room for better early detection and treatment access.[3]

The management of localized PC is based on initial clinical staging, overall health status at diagnosis, and patient values and preferences. The National Comprehensive Cancer Network (NCCN) staging schema utilizes PSA level, TNM status, Gleason grade, and the tumor burden in biopsy cores to assign one of six risk levels which guide treatment selection, balancing disease risk against treatment-related morbidity.[4] The most common curative options include radical prostatectomy (RP), external beam radiation therapy (EBRT), and brachytherapy (radioactive implants at the tumor site). Very low risk disease is safely managed with active surveillance, while watchful waiting is preferred in those with overall poor health status. Pathologic upstaging after RP may lead to adjuvant EBRT and/or chemo-hormonal therapy.[4,5]

Patients with advanced or metastatic disease are candidates for chemo-hormonal therapy. GnRH agonists downregulate pituitary GnRH receptors, thereby reducing the release of luteinizing hormone and testosterone. FDA approval in 1985 of leuprolide had its inception in research performed in the 1940s showing that testosterone suppression with diethylstilbesterol (DES) slowed tumor growth.[6] A 1984 study of 199 men with previously untreated metastatic cancer showed leuprolide to be therapeutically equivalent to DES while reducing important adverse effects, including painful gynecomastia, thromboembolism, and nausea.[7] Surgical castration is a cost-effective alternative to ADT. The advent of GnRH antagonists (e.g., regulolix) for PC has been a more recent development. After approximately 2-3 years, most cancers progress on ADT monotherapy and require additional treatment.[8]

Prior to 2004, mitoxantrone was the chemotherapeutic "treatment of reference" with palliative benefit in metastatic, castrate-resistant prostate cancer but not overall survival (OS). The TAX 327 trial showed that, by comparison, docetaxel conferred a 2-month extension of survival over the 21-month follow-up period (HR for death 0.76; 95% CI: 0.62 to 0.94; p=0.009 by the stratified log-rank test).[9] In 2010, an open label trial of cabazitaxel vs. mitoxantrone in 755 patients who had progressed on docetaxel showed a 2-month extension of survival over the 13-month follow-up period in the cabazitaxel group (HR 0.70; 95% CI: 0.59 to 0.83, p<0·0001).[10]

Abiraterone is an androgen synthesis inhibitor initially approved in 2011 as a second-line treatment for metastatic prostate cancer after failure on docetaxel. Abiraterone was shown to have an earlier role in therapy for ADT-naïve patients with clinical metastases in the 2017 STAMPEDE trial, improving overall survival to 83% over 3 years of follow-up, compared with 76% in the ADT-alone group (HR 0.63; 95% CI: 0.52 to 0.76; p<0.001), an effect paralleled in the contemporaneous LATITUDE trial. Abiraterone is given with prednisolone due to its suppression of adrenal mineralocorticoid production.[11,12]

Androgen receptor pathway inhibitors are used with ADT in therapy for both early metastatic and treatment resistant disease. In the 2012 AFFIRM trial, enzalutamide improved OS for patients whose metastatic disease had progressed after docetaxel. Median OS was 18.4 months (95% CI: 17.3 to not yet reached) with enzalutamide and 13.6 months (95% CI: 11.3 to 15.8) with placebo. At the time of interim analysis, this reflected a 37% reduction in the risk of death vs placebo (HR, 0.63; 95% CI: 0.53 to 0.75; p<0.001).[13] The PREVAIL (2014) and PROSPER (2018) trials showed that enzalutamide improved OS before docetaxel, as well as for patients without metastases who had a rising PSA on ADT monotherapy, respectively.[11] In the 2022 ARASENS trial, darolutamide, when combined with docetaxel and ADT,

became the first ARPI shown to improve OS in patients with high-risk, high-volume hormone sensitive metastatic disease.[14]

Other agents have a role in less common clinical situations, including poly (ADP-ribose) polymerase (PARP) inhibitors (e.g., olaparib, rucaparib) in patients with DNA homologous recombination repair defects including BRCA1, BRCA2 genes, and others; sipuleucel-T in patients with minimally symptomatic; slowly progressive disease; radioligand therapy (e.g. lutetium-177 vipivotide tetraxetan) for treatment-refractory prostate membrane antigen (PSMA) positive disease; and pembrolizumab where germline sequencing demonstrates deficient DNA mismatch-repair.[15]

Bone metastases respond to effective chemo-hormonal therapy, but are treated with EBRT or surgery when 1 or more sites cause pain or threaten function. Zoledronic acid (a bisphosphonate) and denosumab (a RANK ligand inhibitor) can be added for prevention or treatment. Denosumab is often the agent of choice based on evidence from a 2011 blinded comparison to zoledronic acid. Median time to first on-study, skeletal-related event was 20.7 months (95% CI: 18.8 to 24.9) with denosumab compared with 17.1 months (95% CI: 15.0 to 19.4) with zoledronic acid (HR 0.82, 95% CI: 0.71 to 0.95; p=0.0002 for non-inferiority; p=0.008 for superiority).[16] A 2020 Cochrane network meta-analysis concluded that both similarly reduced skeletal-related events, though renal impairment was more likely with zoledronic acid and osteonecrosis of the jaw more likely with denosumab.[17] The radioisotope radium-223 can used for palliation of multifocal bony metastases with no visceral metastases and in the 2013 ALLSYMPCA trial showed a 3-month overall survival benefit, unlike the osteoclast inhibitors (though was studied prior to use of combined antiandrogen therapy). Bone marrow suppression can be a significant adverse effect.[18]

Findings:

Prostate cancer specific mortality does not differ between AI/AN men and Caucasian men despite the fact that AI/AN patients generally present with higher grade, later stage disease. This suggests a health disparity: with earlier diagnosis and improved access to treatment, AI/AN cancer specific mortality might be comparatively lower. GnRH agonists are a mainstay of treatment for advanced and metastatic PC as other agents may be rotated against disease resistance. Leuprolide was therefore added, in any depot formulation, to the National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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