A REVIEW OF PRESENT MANAGEMENT OF CASTRATE RESISTANT PROSTATE CANCER

Author: Chimaobi Gideon Ofoha (MBBS, FWACS)

Division of Urology, Department of Surgery,
College of Medicine, University of Jos/ Jos University Teaching Hospital, Jos Nigeria.
Email: drchimao@yahoo.com.
Phone number: +234803450274

Abstract

Prostate cancer is the most common cancer among Sub-Saharan Africans. Androgen deprivation therapy remains the mainstay for the management of advanced prostate cancer. However, treatment failure is the rule after a predictable response to androgen deprivation with subsequent development of castrate resistant prostate cancer.Several pathways in the propagation of castrate resistant prostate cancer have been elucidated,thus leading to development of novel agents in the management of this otherwise lethal disease.Importantly, most of these cellular alterations still require the presence of some, albeit lower, androgen concentrations. Consequently, it is recommended that ADT be continued for the remainder of a patient's life. This review gives a summary of the current and approved treatment options for castrate resistant prostate cancer.

Keywords

Castrate, resistant, prostate cancer, cytotoxic therapy, Immunotherapy, antiandrogen therapy

Introduction

Prostate cancer is the most common malignancy among males worldwide and is the second leading cause of cancer death among men in the United States. In Sub-Saharan Africans, it is the most common cancer, with a mortality rate more than five times higher than African-Americans.[2 3],

Hormonal treatment based on the findings by Huggins et al. remains the mainstay of treatment for advanced prostate cancer.[45], However, treatment failure is the rule after a predictable response to androgen deprivation with subsequent development of castrate resistant prostate cancer.[6]

Castrate resistant prostate cancer (CRPC) is defined, by the progression of disease despite castrate serum testosterone level (<50 ng/dl or 1.7 nmol/l). It may present as either a continuous rise in serum PSA levels with three consecutive rises in PSA one week apart, with two resulting in 50% increases over the nadir, and PSA >2 ng/ml or progression of an existing disease or the appearance of new lesions [7].

Several mechanisms have been identified as potential explanations for castrate resistant prostate cancer. These include increased sensitivity of the androgen receptor (AR) via gene amplification or over expression, alterations in coregulators that alter ligand sensitivity, androgen receptor (AR) mutations that broaden ligand specificity and confer sensitivity to adrenal androgens, cross-talk via other signalling pathways such as IL-6 and Her2-Neu,nongenomic mechanisms by which ligand-bound AR modulates transcription and alterations in steroid synthetic and androgen-metabolizing enzymes that potentiate intraprostatic androgen production [8,9,10, 11, 12, 13, 14, 15].

Importantly, most of these cellular alterations still require the presence of some, albeit lower, androgen concentrations. Consequently, it is recommended that ADT be continued for the remainder of a patient's life [16].

Clinical scenarios in castrate resistant prostate cancer include patients with rising PSA who are asymptomatic without evidence of metastasis and patients with severe cancer symptoms as a result of metastasis. These clinical situations determine and modify the treatment offered to these patients.

This review gives a summary of the current treatment options and clinical data for the treatment of castrate resistant prostate cancer.

Methodology

A systematic review of the literature was conducted, and articles published on the management of castrate resistant prostate cancer (CRPC) were retrieved. A search of the electronic

databases, including PubMed, Google Scholar and Crossref Metadata Search using the keywords castrate, resistant, prostate cancer, cytotoxic therapy, immunotherapy, antiandrogen therapy. Searches were restricted to publications in the English literature.

Management of Castrate Resistant Prostate Cancer.

Hormonal Manipulation

Patients in the transition phase of CRPC who have been on androgen deprivation therapymay benefit from secondary hormonal manipulation.

These will be in the form of addition of antiandrogen (Bicalutamide, Nilutamide or flutamide) for patients on monotherapy (luteinising hormone releasing hormone analogue) or who have had an Orchidectomy. Antiandrogen can induce a second response in almost 50% of castration-resistant prostate cancer patients. The duration of response is more than 1.5 years on average and responders have prolonged metastasis-free survival.[17, 18, 19]

The withdrawal of antiandrogen for patients who have undergone total androgen blockade, Antiandrogen withdrawal are significantly associated with both longer progression free survival and overall survival in patients with castrate- refractory prostate cancer.

PSA response can be up to 30%. [20, 21, 22]

Ketoconazoleis an inhibitor of testicular and adrenal androgen biosynthesis. It inhibits17α-hydroxylase and 17,20-lyase which convert pregnenolone into androgens, and 11β-hydroxylase, which converts 11-deoxycortisol to cortisol. In a phase trial by Small et al. [23]there was an objective response in patients receiving ketoconazole. Low dose ketoconazole with replacement doses of hydrocortisone has moderate activity.[24]

Non-Metastatic Castrate Resistant Prostate Cancer (m0CRPC)

In this clinical scenario, there is a PSA rise in men who have had curative therapy for prostate cancer without clinical evidence of disease progression. This group of patients present a management conundrum.

There is no generally accepted standard care for this group of patients. Secondary hormonal treatments may be attempted. A recent study by Smith et al. using apalutamide (240mg/day), a competitive inhibitor of the androgen receptor showed significantly longer metastasis free survival and time to symptomatic progression among men with nonmetastatic castration-resistant prostate cancer. The median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group. Time to symptomatic progression was significantly longer with apalutamide than with placebo. [25]

Metastatic Castrate Resistant Prostate Cancer (mCRPC).

Only patients with detectable macroscopic metastatic disease should be considered for systemic therapy (new hormonal agents or chemotherapy). These patients should receive multimodal and multidisciplinary therapy to maximise survival and improve quality of life.

Cytotoxic Chemotherapy.

Mitoxantrone is an antitumor antibiotics that inhibits type topoisomerase. This disrupts both DNA synthesis and DNA repair. It is used for palliation of symptoms, especially pain in men with mCRPC. It does not affect the overall survival of patients or time to disease progression[26] however, there have been questions regarding its use because of the side effects profile. These effects include neutropenia and neutropenic fever, anaemia, fatigue, peripheral neuropathy, back pain and left ventricular dysfunction[27]. However, it is useful in patients who progress after chemotherapy.

Docetaxel, a taxane whose mechanism of actionis believed to be two-fold. This involves the inhibition of microtubule depolymerisation and the attenuation of the effects of bcl-2 and bcl-xL gene expression. The induction of microtubule stabilisation causes cell arrest in the G(2)M phase of the cell cycle and induces bcl-2 phosphorylation, thereby promoting a cascade of events that leads to apoptotic cell death. A landmark study by Tannock et al. in 2004 demonstrated the efficacy of docetaxel in the management of castrate resistant prostate cancer. In this three-arm study, patients were randomised to receive a docetaxel three weekly regimen (75mg/m^2) plus low-dose prednisone (10mg daily), a docetaxel weekly (30mg/m^2 for 5 or 6 weeks) plus prednisone, or mitoxantrone (12mg/m^2 3weekly) plus prednisone.

The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the group given docetaxel every three weeks, and 17.4 months in the group given weekly docetaxel. Among these three groups, 32%, 45% and 48% of men, respectively, had at least a 50% decrease in the serum PSA level. 22%, 35% and 31% had predefined reductions in pain; and 13%, 22% and 23% had improvements in the quality of life. Adverse events were more common in the groups that received docetaxel and the three weekly docetaxel showed better outcome than weekly docetaxel. Adverse effects of docetaxel included neutropenia, fatigue, nausea or vomiting or both, alopecia, diarrhoea, nail changes, sensory neuropathy, anorexia, changes in taste, stomatitis, dyspnoea, tearing, peripheral oedema, and epistaxis.

Cabazitaxel is a taxane. It differs from docetaxel by its weak affinity for P-glycoprotein, an ATP-dependent drug efflux pump. Tumour cells that express the glycoprotein become resistant to taxanes, limiting the effectiveness of docetaxel [28].The FDA approved itfor patients who progress post docetaxel therapy. This was based on the TROPIC study,which compared cabazitaxel and mitoxantrone in patients who progressed after docetaxel therapy. The median survival was 15·1months in the cabazitaxel group and 12·7 months in the mitoxantrone group. Median progression-free survival was 2·8 months in the cabazitaxel group and 1·4 monthsin the mitoxantrone group. The most common clinically significant grade 3 or higher adverse events were neutropenia (cabazitaxel, [82%] patients versus mitoxantrone[58%]) and diarrhoea [6%] versus[<1%]). 8% of the patients in the cabazitaxel group and 1% in the mitoxantrone group had febrile neutropenia [29].

Novel Antiandrogen Therapy.

Abiraterone is a selective, irreversible, and potent inhibitor of 17-[alpha]-hydroxylase/17,20-lyase (CYP17) enzymatic activity which is required for androgen biosynthesis in the testes, adrenal glands, and prostate tissue [30]. Abiraterone iseffective in the pre and post-chemotherapy setting for castrate resistant prostate cancer.In chemotherapy naïve patients, the median radiographic progression free survival was 16.5 months with improvement in overall survival with abiraterone-prednisolone compared to 8.3 months and 27.2months respectively with prednisolone alone. It also showed superiority over prednisone alone concerning time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain and prostate-specific antigen progression[31]. In patients receiving abiraterone acetate-prednisolone post chemotherapy with docetaxel, after a median follow-up of 12.8 months, overall survival was longer in the abiraterone acetate–prednisone group than in the placebo–prednisone group (14.8 months vs 10.9 months). PSA progression (10.2 vs. 6.6 months), progression-free survival (5.6 months vs. 3.6 months), and PSA response rate (29% vs. 6%). The improved parameters favoured the treatment group.Adverse events were frequently recorded in the abiraterone acetate-prednisolone group than the placebo-prednisolone group[32]. These included fluid retention, hypertension, and hypokalaemia.

Enzalutamide is a potent, competitive inhibitor of the androgen receptor. It also preventstranslocation of the AR from the cytoplasm to the nucleus and inhibits DNA binding, thereby impairing tumour growth. It is useful in the pre and post-chemotherapy setting. It showed obvious benefits in chemotherapy naïve patients as demonstrated by Beer et al [33]. In their study, comparing enzalutamide and placebo, the radiographic progressionfree survival at 12 months was (65% vs 14%), overall survival was (63% vs 29%). Other recorded benefitsinclude time to initiation of cytotoxic chemotherapy, the time to first skeletal-related event, a complete or partial soft-tissue response (59%vs.5%), the time to prostate-specific antigen (PSA) progression and PSA decline (78% vs 3%). Hypertension and fatigue were recorded adverse effects. In patients who have received prior chemotherapy, enzalutamide showed benefits compared to placebo. The median overall survival was 18.4 months compared to 13.6 months, reduction in the prostate-specific antigen (PSA) level by 50% or more (54% vs 2%), soft-tissue response rate (29% vs 4%), the quality-of-life response rate (43% vs 18%), the time to PSA progression (8.3 vs 3.0 months), radiographic progression-free survival (8.3 vs 2.9months) and the time to the first skeletal-related event(16.7 vs.13.3months). Adverse effects recorded includedfatigue, diarrhoea, hot flashes and seizures [34].

Immunotherapy

The immune system can respond to prostate cancer antigens. Presently there are ranges of immunotherapeutic strategies which are being developed and evaluated. The goal is the induction of de novo response or reactivation of antitumor immune responses[35].

Sipuleucel-T, an autologous cellular immunological agent, approved for clinical use, works through antigen presenting cells (dendritic cells) to stimulate T-cell immune response targeted against prostatic acid phosphatase (PAP), an antigen that is highly expressed in most prostate cancer cells.[36,27] In a study involving patients with asymptomatic metastatic castrate resistant prostate cancer, in which sipuleucel-T was compared with placebo. The median time for disease progression for sipuleucel-T was 11.7 weeks compared with 10.0 weeks for placebo. Median survival was 25.9 months for sipuleucel-T and 21.4 months for placebo. Thisstudy suggests that sipuleucel-T may provide a survival advantage to asymptomatic patients with metastatic castrate resistant prostate cancer.[38] In another study, treatment with sipuleucel-T resulted in a 4.1-month improvement in median survival and an improvement in the rate of 3-year survival (31.7% for patients receiving sipuleucel-T, as compared with 23.0% for those receiving placebo) [39].

Bone Targeted therapy

Patients with castrate resistant prostate cancer will ultimately develop skeletal related events; bone pain, pathological fracture, nerve compression syndromes and spinal cord compression. These events will occur in over 90% of the patientswho have been on androgen deprivation therapy for excess of ten years,and it is due to the effect of androgen deprivationtherapy on bone mineralisation and bone metastases [40].

Bisphosphonates are protective against skeletal related events. They act by integration into the bone matrix, by binding to hydroxyapatite crystals, with resultant inhibition of osteoclast-mediated bone resorption [41]. Zoledronic acid is the only bisphosphonate that is effective in reducing skeletal related events in men with castrate resistant prostate cancer. In a phase III trial, in which patients were randomised into zoledronic acid and placebo, a higher proportion of patients who received placebo had skeletal-related events than those who received zoledronic acid(44.2% versus 33.2%). The median time to first skeletal-related event was 321 days for patients who received placebo, while it was not reached for patients who received zoledronic acid. Compared with urinary markers in patients who received placebo, urinary markers of bone resorption were statistically significantly decreased in patients who received zoledronic acid. Pain and analgesic scores increased more in patients who received placebo than in patients who received zoledronic acid. Zoledronic acid at 4 mg given as a 15-minute infusion was well tolerated, but the 8-mg dose was associated with renal function deterioration.[42, 43] Other side effects include flu-like symptoms, hypocalcaemia and osteonecrosis of the jaw bone.

Denosumab is a fully human monoclonal antibody that binds RANKL, preventing RANKL from activating RANK, thereby inhibiting osteoclast activity. These decreases bone resorption and subsequently increases bone mass [44].

Denosumab was better than zoledronic acid for the prevention of skeletal-related events, and potentially represents a novel treatment option in men with bone metastases from castration-resistant prostate cancer.[45] The median time to first on-study skeletal-related event was 20·7 months with denosumab compared with 17·1months with zoledronic acid. Side effects of denosumab includedosteonecrosis of the jaw, hypocalcaemia

Radium-223 is a radioactive isotope.It mimics calcium in forming complexes with the bone mineral hydroxyapatite, which targets explicitly bone metastases.It prefers new bone around metastatic sites emitting lethal alpha particles in the tumour microenvironment which leads to doublestranded DNA damage, thereby inhibiting tumour growth.[46,47]

In a phase III trialwith radium-223,the median overall survival was 14.0 months in the radium-223 group and 11.2 months in the placebo group. Radium-223, as compared with placebo, was associated with a 30% reduction in the risk of death. The effect of radium-223 on overall survival was consistent. The risk for time to first symptomatic skeletal event was reduced, good PSA and alkaline phosphatase responses were noted.[48,49]It showed a low myelosuppressive effect.

Table 1: Summary of Clinical Management of Metastatic Castrate Resistant Prostate Cancer

S/N	Clinical Scenario	Recommended Treatment
1	Metastatic CRPC without Symptoms	Abiraterone acetate 1000 mg/day plus prednisone 5mg /twice daily. Enzalutamide 160mg/day. Docetaxel 75mg/m ^{2} every 3weeks plus oral prednisone 5mg twice daily.
2	Metastatic CRPC with Symptoms	Docetaxel 75mg/m ^{2} every 3weeks plus 5mg oral prednisone twice daily for 10cycles. Radium-223 every 4weeks for 6cyclesin patients with pain due to bone me tastases without visceral metastases. Abiraterone acetate 1000mg/d plus prednisone 5mg twice daily or E nzalutamide 160 mg/d may be considered as first -line therapy in patients who cannot receive or refused docetaxel
3	Metastatic CRPC who Progress after Docetaxel-Based Chemotherapy	Cabazitaxel (25mg/m^2) plus prednisone (5mg/day). Abiraterone acetate (1000 mg per day) plus prednisone (5mg twice daily). Enzalutamide (160mg/day) Radium-223 every 4weeks for 6cycles. Docetaxel plus prednisone re -exposure. (Positive initial response). Mitoxantrone plus prednisone for palliative pain relief.
4	Patients with CRPC and Bone Metastases	Denosumab (120mg subcutaneous) or zoledronic acid (4mg intravenous) every 4weeks. Daily calcium and vitamin D supplementation

PalliativeCare.

Castrate resistant prostate cancer is a progressive disease and patient will ultimately succumb to the disease process. Disease progression is epitomised by pain, obstructive uropathy, bone fractures, anaemia, coagulopathy and fatigue. Improving the quality of life of the patient and that of the caregiver is of paramount importance. Realistic goals should be set for patient care. Aggressive therapy without justifiable product should be avoided. Patient should receive adequate pain control with judicious use of analgesics (using the analgesic ladder) [50], adjuvant analgesics and steroids. Specific therapy, such as stenting, surgical decompression and radiation therapy where necessary, will provide succour and relief. Psychological, physical and spiritual support should be provided [51].

Conclusion

Castrate resistance prostate cancer is a grin disease with grave consequences for the patient. Treatment of this disease is rapidly evolving with overall survival and progression free survival in the region of months with current modalities oftreatment. Hopefully, current researches will come up with newer treatment modalities that will improve survival and improve the quality of life of patients.

References

1. Bashir MN. Epidemiology of Prostate Cancer. Asian Pac J Cancer Prev. 2015;16(13):5137-41.
2. Rebbeck TR, Devesa SS, Chang BL, et al. Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of African descent. Prostate Cancer 2013;2013:560857.

3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008," Int J of Cancer. 2010; 127(12): 2893–2917.
4. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of oestrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol. 2002; 168(1):9-12.
5. Huggins C, Stevens RE, Hodges CV. Studies on Prostate Cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg. 1941;43:209–23.
6. Kantoff PW, Carroll PR, D'Amico AV. Prostate cancer: principles and practice. Philadelphia: Lippincott Williams & Wilkins, 2002
7. Saad F, Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. Can Urol Assoc J 2010;4(6):380-384
8. Bubendorf L, Kononen J, Koivisto P, et al. Survey of gene amplifications during prostate cancer progression by high-throughout fluorescence in situ hybridization on tissue microarrays. Cancer Res 1999;59:803–806.
9. Gregory CW, He B, Johnson RT, et al. A mechanism for androgen receptor-mediated prostate cancer recurrence after androgen deprivation therapy. Cancer Res 2001;61:4315–4319.
10. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. Nat Med 2004;10:33–39.
11. Mizokami A, Koh E, Fujita H, et al. The adrenal androgen androstenediol is present in prostate cancer tissue after androgen deprivation therapy and activates mutated androgen receptor. Cancer Res 2004;64:765–771.
12. Ueda T, Bruchovsky N, Sadar MD. Activation of the androgen receptor N-terminal domain by interleukin-6 via MAPK and STAT3 signal transduction pathways. J Biol Chem 2002;277:7076–7085.
13. Li P, Lee H, Guo S, Unterman TG, Jenster G, Bai W. AKT-independent protection of prostate cancer cells from apoptosis mediated through complex formation between the androgen receptor and FKHR. Mol Cell Biol. 2003;23: 104–118.
14. Harkonen P, Torn S, Kurkela R, et al. Sex hormone metabolism in prostate cancer cells during transition to an androgen-independent state. J Clin Endocrinol Metab. 2003;88:705–712.
15 Holzbeierlein J, Lal P, LaTulippe E, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol 2004;164 :217–227.
16. Elahe AM, Stephanie TP, Daniel WL, Ladan F, Ilsa MC, Lawrence DT. Et al. Intraprostatic Androgens and Androgen-Regulated Gene Expression Persist after Testosterone Suppression: Therapeutic Implications for Castration-Resistant Prostate Cancer. Cancer Res 2007; 67(10):5033–5041.
17. Lodde M, Lacombe L, Fradet Y. Salvage Therapy with Bicalutamide 150 mg in Nonmetastatic Castration-resistant Prostate Cancer. Urology 2010;76 (5):1189-1193.
18. Kassouf W, Tanguay S, Aprikian AG. Nilutamide as Second Line Hormone Therapy for Prostate Cancer After Androgen Ablation Fails.The Journal of Urology 2003; 169 (5): 1742-1744.
19 Qian SB, Shen HB, Cao QF, Zhang L, Chen YF, Qi J. Bicalutamide 150 mg as secondary hormonal therapy for castration-resistant prostate cancer. Int Urol Nephrol. 2015;47 (3):479-84.
20. Sartor AO, Tangen CM, Hussain MH, Eisenberger MA, Parab M et al. Antiandrogen Withdrawal in Castrate-refractory Prostate Cancer. Cancer. 2008; 112(11): 2393–2400.
21. Anantharaman A, Friedlander TW. Targeting the androgen receptor in metastatic castrate-resistant prostate cancer: a review. Urol Oncol. 2016;34 (8):356–67.
22. Hotte SJ, Saad F. Current management of castrate-resistant prostate cancer. Curr

Oncol. 2010; 17(Suppl 2): S72–S79.
23. Small EJ, Halabi S, Dawson NA, Stadler WM, Rini BI et al Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial. J Clin Oncol. 2004; 22(6):1025-1033.
24. Harris KA, Weinberg V, Bok RA, Kakefuda M, Small EJ. Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer. J Urol. 2002; 168 (2):542-545.
25. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378 (15):1408-1418.
26 Kantoff PW, Halabi S, Conaway M, Picus J, Kirshner Jet al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol. 1999;17(8):2506-13.
27. Green AK, Corty RW, Wood WA, Meeneghana M, Reeder-Hayesa KE et al. Comparative Effectiveness of Mitoxantrone plus Prednisone Versus Prednisone Alone in Metastatic Castrate-Resistant Prostate Cancer After Docetaxel Failure. The Oncol. 2015; 20(5): 516-522
28. Paller CJ, Antonarakis ES. Cabazitaxel: a novel second-line treatment for metastatic castration-resistant prostate cancer. Drug Des Devel Ther. 2011; 5: 117–124.
29. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet. 2010; 376(9747):1147-1154.
30. Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol. 2008; 26(28):4563–4571
3. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-48.
32. De Bono J., Logothetis C., Molina A., Fizazi K., North S., Chu L., et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011; 364(21): 1995–2005
33. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS et al. Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N Engl J Med. 2014 July 31; 371(5): 424–433.
34. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 ;367(13):1187-1197.
35. Quinn DI, Shore ND, Egawa S, Gerritsen WR, Fizazi K. Immunotherapy for castration-resistant prostate cancer: Progress and new paradigms. Urol. Oncology: Seminars and Original Investigations. 2015; 33(5):245-260.
36. Anassi E, Ndefo UA. Sipuleucel-T (Provenge) Injection.The First Immunotherapy Agent (Vaccine) For Hormone-Refractory Prostate Cancer. P T. 2011; 36(4): 197–202
37. Antonarakis ES, Drake CG. Review Current status of immunological therapies for prostate cancer.
Curr Opin Urol. 2010; 20(3):241-6
38. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006;24(19):3089-3094
39. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. N Engl J Med 2010; 363(5):411-422
40. Morote J, Morin JP, Orsola A, Abascal JM, Salvador C et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology. 2007;69(3):500-504.
41. Saad F. Bone-targeted therapy in prostate cancer. EJC Suppl. 2013;11(2): 257–259.

42. Saad F, Gleason DM, Murray R. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94(19):1458–1468.
43. Saad F, Gleason DM, Murray R. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96(11):879–882
44. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab. 2011; 96(4):972-980.
45. Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813–822.
46. Shore ND. Radium-223 Dichloride for Metastatic Castration-resistant Prostate Cancer: The Urologist's Perspective. Urology. 2015; 85(4): 717-724
47. Henriksen G, Fisher DR, Roeske JC, et al. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. J Nucl Med.2003: 44(2): 252-259
48. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. N Engl J Med 2013; 369:213-223
49. Hoskin P, Sartor O, O'Sullivan JM, Johannessen DC, Helle SI et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol. 2014;15(12):1397-1406.
50. Hanks GW, De Conno F, Cherny N, Hanna M, Kalso E et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001; 84(5): 587–593.
51. Kaya E, Feuer D. Prostate cancer: palliative care and pain relief. Prostate Cancer Prostatic Dis. 2004;7(4):311-315.