Treatment sequencing in mCRPC improves outcomes for patients with progressive mCRPC

The optimal sequencing of systemic therapy for the management of metastatic castration-resistant prostate cancer (mCRPC) remains poorly elucidated and has been the topic of considerable discussion.[1,2] During the PROSPECT (Prostate Cancer Patient Case Exchange Taskforce) Series 2 experts' discussion organised by Johnson & Johnson, Dr Letran shared his clinical experience in the management of progressive mCRPC. Other distinguished speakers present in the meeting were Dr Takashi Kawahara, Prof Dr Rainy Umbas and Assoc Prof Dr Worapat Attawettayanon.

Dr Jason Letran

Director
Cancer Institute & Urology Institute;
Chinese General Hospital & Medical Centre,
Philippines

Patient presentation and management

In 2014, a 76-year-old male patient presented with:

- Prostate-specific antigen (PSA) level of 101.5 ng/dL
- Gleason Score of 9 (5+4)
- Testosterone level of 306 ng/dL
- Mild lower urinary tract symptoms

The patient had a history of:

- Hypertension
- Type 2 diabetes
- Cerebrovascular accident
- Seizures

A bone scan revealed that he had multiple osseous metastases, while magnetic resonance imaging (MRI) did not detect any lymph node or visceral metastasis.

The patient was started on androgen deprivation therapy and he maintained good PSA control for the next 21 months (PSA nadir of 0.4 ng/dL). Subsequently, the patient developed gradually rising PSA levels of up to 12.1 ng/dL, but bone scan and MRI did not detect any changes.

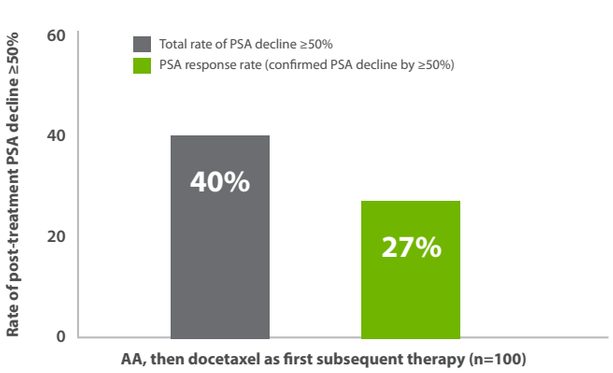
First-line treatment options for mCRPC

The choice of treatment for older adults should be individualised, guided by patient's expectations, clinical profile and comorbidities.[3,4] On account that the patient was largely asymptomatic and had no visceral metastasis, novel hormonal therapy (NHT) was preferred over chemotherapy.[5] Moreover, special considerations such as minimising the use of immunosuppressive cancer treatments had to be made during the coronavirus disease 2019 (COVID-19) pandemic.

In a large retrospective, real-world study, patients who received abiraterone acetate (AA) were less likely to experience a central nervous system event compared with those who received enzalutamide (ENZ) (39.5% vs 46.0%, respectively; p=0.0036) or chemotherapy (39.5% vs 51.1%, respectively; p=0.0277).[6]

Additionally, the results of the AQUARiUS study revealed that patients treated with AA experienced significantly less fatigue and cognitive impairments compared with those treated with ENZ.[7] Therefore, owing to the patient's advanced age and history of seizures, AA plus prednisolone was preferred over ENZ monotherapy.

Figure. Total and confirmed post-treatment PSA decline from subsequent docetaxel therapy[10]



Clinical outcome and second-line agents

The patient tolerated AA therapy well and achieved good PSA response, which lasted for 18 months before patient's cancer started to progress; his PSA levels started rising again and MRI revealed multiple nodal metastases. In patients who have progressed on an NHT, docetaxel is the preferred second-line agent regardless of whether the patient is symptomatic or not.[8,9] A post hoc analysis of COU-AA-302* showed that patients with mCRPC who had progressed on AA therapy may still derive benefit from subsequent docetaxel therapy (**Figure**).[10]

1 When would you send a tumour sample for genetic testing and what is its significance?

Insight from Dr Letran

DNA damage repair defects affect approximately 20% of mCRPC patients, with *BRCA2* mutations representing the most frequent event. Recent studies have shown that *BRCA* mutations predict good response to poly-ADP ribose polymerase (PARP) inhibitors, such as olaparib, rucaparib, and niraparib.[11] In my practice, I will send a sample for genetic testing upon the diagnosis of mCRPC to test for *BRCA1/2* gene alterations. If these targetable genetic alterations are identified, the patient can be initiated on a PARP inhibitor first, thus prolonging the chemotherapy-free interval.

2 How does the COVID-19 vaccination impact treatment with AA plus prednisolone?

Insight from Prof Dr Umbas

Prioritised vaccination among patients with cancer has been recommended globally.[12] However, there have been concerns about the effect of prednisolone, administered in combination with AA, on patients' immune response postvaccination.[13]

In my practice, we postpone the initiation of AA plus prednisolone therapy among patients who have not completed their COVID-19 vaccinations. AA treatment is started 1 month after the second COVID-19 vaccination is administered. Alternatively, the patient can be initiated on ENZ instead, as it is not prescribed with a glucocorticoid. However, if the patient has already been stable on AA therapy and is planning to receive their COVID-19 vaccination, I will pause their treatment for 6 weeks after the vaccine administration.

KEY TAKEAWAYS

- In the past, first-generation anti-androgens have been the standard approach to treating mCRPC.[14]
- However, recent phase III studies have demonstrated better clinical outcomes with the use of chemotherapy (docetaxel and cabazitaxel), NHT (AA and ENZ), sipuleucel-T, radium-223, and olaparib.[14,15]
- Treatment sequencing should be individualised based on patient's clinical profile and comorbidities.[3,4]

***COU-AA-302,** AA plus prednisone versus placebo plus prednisone in chemotherapy-naive men with mCRPC

References: 1. Andrews JR, et al. *Prostate* 2020;80:399–406. 2. McNeel DG, et al. *J Immunother Cancer* 2016;4:92. 3. Morgans AK, et al. *Am Soc Clin Oncol Educ Book* 2017;37:370–381. 4. Hall WH, et al. *Prostate Cancer Prostatic Dis* 2005;8:22–30. 5. National Comprehensive Cancer Network (NCCN). 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 1 Nov 2021. 6. Pilon D, et al. *Am Health Drug Benefits* 2017;10:143–153. 7. Thiery-Vuillemin A et al. *Eur Urol* 2020;77:380–387. 8. González Del Alba A, et al. *Clin Transl Oncol* 2021;23:969–979. 9. Maluf FC, et al. *JCO Glob Oncol* 2021;7:559–571. 10. de Bono JS, et al. *Eur Urol* 2017;71:656–664. 11. Messina C, et al. *J Oncol* 2020;2020:4986365. 12. Liontos M, et al. *Prostate Cancer and Prostatic Diseases* 2021. Available at: https://www.nature.com/articles/s41391-021-00455-9#citeas. Accessed on 01 December 2021. 13. STAMPEDE Trial. Information on COVID-19. Available at: http://www.stampedetrial.org/centres/information-on-covid-19/. Accessed on 01 December 2021. 14. Leung DK, et al. *Biomedicines* 2021;9:339. 15. Powers E, et al. *J Hematol Oncol* 2020;13:144.

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Johnson&Johnson
SOUTHEAST ASIA

MY-JJ-028