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Abiraterone: moving up in line?

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The crucial role of testosterone in the growth and dissemination of prostate cancer has been well known for over six decades. In his 1966 *Nobel Lecture*, Charles Huggins described how in his clinical studies, he discovered that endocrine manipulation, either by castration or oestrogen administration, led to a significant increase in appetite, and a decrease in pain in patients with advanced prostate cancer.[1] By using this approach, Huggins became the first clinician to provide an effective, systemic antihormonal treatment for patients with prostate cancer.

Nowadays, androgen deprivation therapy (ADT) is still the cornerstone of the treatment of metastatic prostate cancer. By lowering serum testosterone levels to castrate levels using luteinising hormone-releasing hormone agonists, androgen receptor (AR) driven tumour growth is blocked and most patients observe a rapid improvement in symptoms and decrease in prostate specific antigen (PSA). Unfortunately, despite these initial marked improvements, resistance to ADT gradually occurs with the emergence of metastatic castration-resistant prostate cancer (mCRPC), typically after 1–2 years of treatment.

The growth of prostate cancer cells despite castrate levels of testosterone led to the hypothesis that extragonadal and extra-adrenal sources of testosterone might contribute to AR activation and subsequent tumour growth. Proof of intratumorous testosterone synthesis was first shown by Attard *et al*.[2] It was demonstrated that weak androgens such as dehydroepiandrosterone and androstenedione can be converted to AR activating testosterone by cytochrome P450 enzymes CYP11A1 and CYP17A1, findings that eventually led to the development of the specific CYP17A1 inhibitor abiraterone.

In September 2011, the European Commission granted the marketing authorisation of abiraterone acetate (Zytiga) with either prednisone or prednisolone for the treatment of mCRPC after failure of chemotherapy with docetaxel after abiraterone showed superiority over placebo on all primary and secondary end points in a preplanned interim analysis of the COU-AA-301 trial.[3] The subsequent COU-AA-302 trial demonstrated similar superiority over placebo in patients with progressive mCRPC who had not received chemotherapy,[4] leading to marketing authorisation in December 2012 due to this indication.

After the two major successes for abiraterone, the results from the phase III LATITUDE trial are likely to yield yet another paradigm change in the treatment landscape of metastatic prostate cancer. In this trial, ADT plus abiraterone and prednisolone was associated with significantly higher rates in terms of overall survival (OS) when compared with ADT alone in patients with high-risk metastatic hormone-sensitive prostate cancer (not reached vs 34.7 months) (HR for death, 0.62; 95% CI, 0.51 to 0.76, P<0.001).[5]

Whether all patients should now receive upfront combination therapy with ADT and abiraterone rather than the upfront addition of docetaxel, remains a topic of discussion. A recent meta-analysis, performing an indirect comparison of data from five randomised phase III clinical trials on ADT±abiraterone or docetaxel in the hormone-sensitive setting, suggests marginal superiority of abiraterone+ADT over docetaxel+ADT regarding both OS (HR 0.62 vs 0.73) and progression free survival (HR 0.38 vs 0.63),[6] but the lower incidence of side effects affecting quality of life make abiraterone an attractive new treatment option in the first-line treatment of hormone-sensitive advanced or metastatic setting. Further studies focusing on the selection of the ideal drug or combination for each individual patient, based on both clinical data, and taking into account novel predictive biomarkers such as the AR splice variant-7, are eagerly awaited.

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