Research Review
PRODUCT REVIEW

Abiraterone acetate [Zytiga®]

About the Reviewer

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Dr Fong is a Consultant Medical Oncologist at Auckland City Hospital, where he was the Team Lead in genitourinary medical oncology from 2008–13. He has a keen interest in the medical oncologist's role in the treatment of castration-resistant prostate cancer. He is an Honorary Academic at the University of Auckland. He also works at Canopy Cancer Care.

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ABOUT RESEARCH REVIEW

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

Product Reviews feature independent short summaries of major research affecting an individual medicine or technique. They include a background to the particular condition, a summary of the medicine and selected studies by a key New Zealand specialist with a comment on the relevance to New Zealand practice. Research Review publications are intended for New Zealand medical professionals.

This review discusses the evidence in support of the use of oral abiraterone acetate [Zytiga®] as combination therapy with prednisone/prednisolone in the treatment of patients with metastatic advanced prostate cancer (castration-resistant prostate cancer, mCRPC). From 1 May 2015, PHARMAC is funding abiraterone acetate 250 mg tablets, subject to Special Authority criteria, for men with mCRPC that is resistant to ADT. This publication has been supported by Janssen. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of Janssen.

In New Zealand, abiraterone acetate is indicated with prednisone or prednisolone for the treatment of men with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated, and also for men with mCRPC who have received prior chemotherapy containing a taxane.[1]

Data from two phase III trials have demonstrated that abiraterone acetate is a well-tolerated once-daily medication that benefits most patient groups in the treatment of mCRPC, improving progression-free survival (PFS) in both chemotherapy-naïve men with progressive mCRPC and in those previously treated with docetaxel.[2,3] Long-term safety data for abiraterone acetate in the treatment of mCRPC have not identified any new safety concerns.

The burden of prostate cancer

Prostate cancer is a significant public health problem. As one of the four most common cancers (i.e., lung, female breast, bowel and prostate cancer), this condition accounted for an estimated 8% of all cancers diagnosed worldwide and an estimated 8% of all deaths from cancer in 2012.[4]

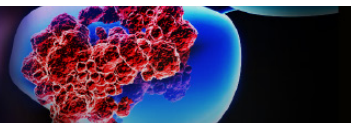
Lifetime prostate cancer costs are high. A recent economic analysis conducted in the US estimated lifetime total medical care costs of $US110,520 per patient and disease-related per-patient lifetime medical care costs in excess of $US30,000 among men diagnosed with prostate cancer at ≥65 years of age.[5] Aggregate life-time total costs for all incident cases ≥65 years and diagnosed in the US during 2008 were $12.4 billion.[5] Aggregate costs associated with prostate cancer-related medical care totalled approximately $3.9 billion.[5] Moreover, this analysis makes the point that higher resource costs associated with treatment advances in advanced prostate cancer are likely to understate the initial and lifetime treatment costs for prostate cancer patients diagnosed today.[5]

In addition, the disease manifestations of prostate cancer cause significant morbidity. A prostate cancer clinical-states model, developed as a framework for patient management and drug development, depicts the continuum from diagnosis to development of clinical metastases as being marked by a sequence of events associated with deterioration of overall health and worsening symptoms: beginning with clinically localised disease, followed by rising prostate-specific antigen (PSA)/a non-castrate disease state, developing into clinical metastases/a non-castrate disease state or rising PSA/castrate disease, then clinical metastases/castrate disease and death from disease.[6]

Treatment options

Cure is often achieved in early-stage prostate cancer by using definitive primary treatment with surgery and radiation.[7] As many as 10–20% of men with prostate cancer present with metastatic disease at diagnosis and 20–30% of patients diagnosed with localised disease eventually develop metastases.[7] Deaths from prostate cancer are typically due to mCRPC (defined by tumour growth despite castrate levels of testosterone, <50 ng/dL [1.7 nmol/L]) and historically the median survival for men with mCRPC has been less than 2 years.[8] However, novel treatments for mCRPC that have become available over the last decade have dramatically changed the treatment of men with mCRPC, minimising adverse effects from this disease and prolonging survival.[8]

Up until 2004, patients who failed primary ADT could only be treated for palliative purposes, in the absence of any treatment proven to increase survival for men with mCRPC.[7,8] In 2004, a combination docetaxel/prednisone regimen was approved for the management of patients with mCRPC, based on the evidence from two landmark phase III trials (TAX 327 and SWOG 9916) demonstrating a survival benefit of approximately 2 months for docetaxel in combination with either prednisone or estramustine.[7] The docetaxel/prednisone regimen became the standard first-line therapy.[7] Subsequent clinical investigations have focused on improving the efficacy of docetaxel and prolonging its therapeutic benefit.[7] Up until 2010, no treatment options were available



that conferred a survival benefit in patients with docetaxel-refractory CRPC; mitoxantrone was often used in this setting for its palliative effects on bone pain.[7]

Improved understanding of the tumour biology in mCRPC has led to the development of novel therapeutic agents designed to further decrease androgen production or block androgen receptor function.[8] Androgen-based pathways play a crucial role in the progression of mCRPC.[9] Other mechanisms include adrenal and intratumoural androgen production via upregulation of cytochrome P450 17 alpha-hydroxysteroid dehydrogenase (CYP17).[9] Anti-tumour activity has been reported in mCRPC with the use of ketoconazole, an inhibitor of CYP17.[10] However, the non-specificity of this drug required high doses to inhibit CYP17, resulting in a high incidence of grade 3 or 4 adverse events.[10]

Abiraterone acetate was therefore developed as a selective, irreversible inhibitor of CYP17 and has proven to be both more potent and selective than ketoconazole.[9]

Management of patients with metastatic prostate cancer in New Zealand

Results from two recent investigations conclude that ADT and chemotherapeutic agents are under-utilised in New Zealand men with advanced prostate cancer.[11,12]

The first study used the New Zealand Cancer Registry to identify 15,947 men diagnosed with prostate cancer between 2006 and 2011.[11] A total of 4978 (31%) were prescribed ADT or chemotherapeutic agents. ADT was dispensed for 72% of men with metastatic disease. Only 24 (0.2%) men received chemotherapeutic agents. Compared with younger men, those aged >70 years with advanced (regional or metastatic) disease were more likely to receive anti-androgens only and to be treated with orchidectomy. Māori and Pacific men (compared with non-Māori/non-Pacific men) were more likely to receive pharmacological ADT, and Māori men were also more likely to be treated with orchidectomy.

The second study sought to characterise New Zealand men diagnosed with metastatic prostate cancer, describe their management and examined their survival.[12] Using the New Zealand Cancer Registry in the Midland Cancer Network region in 2009–2012, the study researchers identified 2127 men diagnosed with prostate cancer, of whom 234 (26 Māori/Pacific and 208 non-Māori/non-Pacific) had metastatic prostate cancer. Post-diagnosis, 194 (82.9%) patients received ADT, 5 had chemotherapy and 104 (44.4%) had radiotherapy. Of the patients treated with ADT, 46 (23.7%) had no monitoring PSA tests. Fifty-nine percent of the patients were alive after 12 months and 35% after 24 months. The hazard ratio for the Māori/Pacific men was 1.49. The study researchers note that the survival of patients with metastatic prostate cancer was poor and they call for the development of New Zealand guidelines on the management of metastatic disease including the use of first-line treatments, the ongoing monitoring for the development of CRPC and the treatment of CRPC.

Funding of abiraterone acetate

PHARMAC's decision to fund abiraterone acetate is predicted to enable up to 1000 men with advanced prostate cancer to receive funded abiraterone acetate annually, either before or after they have received chemotherapy.[13] Subject to Special Authority criteria, abiraterone acetate 250 mg tablets will be listed in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 May 2015. The Wastage rule will be applied to dispensings of abiraterone acetate in Section B of the Pharmaceutical Schedule from 1 May 2015.

Abiraterone acetate – Retail Pharmacy – Specialist Special Authority for Subsidy

Initial application only from a Medical Oncologist, Radiation Oncologist or Urologist or any other medical practitioner on the recommendation of a Medical Oncologist, Radiation Oncologist or Urologist. Approvals valid for 5 months for applications meeting the following criteria:

All of the following:

1. Patient has prostate cancer; and
2. Patient has metastases; and
3. Patient's disease is castration resistant; and
4. Either:
   - 4.1. All of the following:
     - 4.1.1. Patient is symptomatic; and
     - 4.1.2. Patient has disease progression (rising serum PSA) after second line anti-androgen therapy; and
     - 4.1.3. Patient has ECOG* performance score of 0-1; and
     - 4.1.4. Patient has not had prior treatment with taxane chemotherapy; or
   - 4.2. All of the following:
     - 4.2.1. Patient's disease has progressed following prior chemotherapy containing a taxane; and
     - 4.2.2. Patient has ECOG* performance score of 0-2; and
     - 4.2.3. Patient has not had prior treatment with abiraterone.

Renewal only from a Medical Oncologist, Radiation Oncologist or Urologist or any other medical practitioner on the recommendation of a Medical Oncologist, Radiation Oncologist or Urologist. Approvals valid for 5 months for applications meeting the following criteria:

All of the following:

1. Significant decrease in serum PSA from baseline; and
2. No evidence of clinical disease progression; and
3. No initiation of taxane chemotherapy with abiraterone; and
4. The treatment remains appropriate and the patient is benefiting from treatment.

ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen

*ECOG performance status is defined as follows:[14]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but a mbulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Pharmacological properties of abiraterone acetate

Abiraterone, the active metabolite of abiraterone acetate, selectively inhibits the products of the CYP17 gene (17α-hydroxylase and $C_{17,20}$-lyase), which are required for androgen biosynthesis.[1,9]

CYP17 inhibition results in a reduction in cortisol levels and an elevation in adrenocorticotrophic hormone (ACTH) levels, influencing elevations in deoxycorticosterone and corticosterone levels and leading to secondary increases in mineralocorticoids that account for treatment-related side effects such as hypokalaemia, hypertension and fluid retention or oedema.[1,9] Concomitant administration of abiraterone acetate with low-dose prednisone or prednisolone is required to reduce the incidence and severity of the treatment-related elevations in ACTH and associated symptoms.[1,9]

Dosage and administration[1]

The recommended dosage of abiraterone acetate is 1000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food. Abiraterone acetate should be taken at least two hours after eating and no food should be eaten for at least one hour after taking abiraterone acetate. The tablets should be swallowed whole with water.

High variability in the absorption of abiraterone acetate has been observed when administered with food, with up to a 17-fold increase in absorption depending on the fat content of the meal.[1] This potential effect of food on absorption is why abiraterone acetate must not be taken with meals.[1]

Abiraterone acetate is used with low-dose prednisone or prednisolone. The recommended dosage of prednisone or prednisolone is 10 mg daily.

Patients started on abiraterone acetate who were receiving a luteinising hormone-releasing hormone (LHRH) agonist should continue to receive a LHRH agonist.

No dosage adjustment is necessary for patients with pre-existing mild (Child–Pugh class A) hepatic impairment. Abiraterone acetate should be used with caution in patients with moderate (Child–Pugh class B) hepatic impairment, only if the benefit clearly outweighs the possible risk. Abiraterone acetate should not be used in patients with severe (Child–Pugh class C) hepatic impairment.

The adjacent table describes which monitoring steps are necessary when administering abiraterone acetate.

Monitoring patients on abiraterone acetate[1]	
Blood pressure	Ensure normal levels before commencing treatment Monitor at least monthly
Serum potassium	Ensure normal levels before commencing treatment Monitor at least monthly Monitor patients with low potassium levels and/or history of hypokalaemia at least weekly
Fluid retention	Monitor at least monthly
Liver function	Measure serum transaminase and bilirubin prior to commencing treatment then: ▪ First 3 months of treatment – measure every 2 weeks ▪ Subsequent months of treatment – measure monthly Measure serum ALT immediately should symptoms or signs of hepatotoxicity develop

Potential drug interactions

In vitro investigations using human hepatic microsomes have shown that abiraterone acetate is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8, and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.[1] However, when abiraterone acetate plus prednisone were co-administered with a single dose of the CYP1A2 substrate theophylline, there was no increase in systemic exposure of theophylline.[1]

Co-administration of abiraterone acetate plus prednisone with a single dose of the CYP2D6 substrate dextromethorphan approximately doubled the systemic exposure (AUC) of dextromethorphan, while the AUC_{24} value for dextrorphan, the active metabolite of dextromethorphan, was increased approximately by 33%. Thus, caution is advised if co-administering abiraterone acetate with CYP2D6 substrates that have a narrow therapeutic index (e.g., thioridazine) and a dose reduction of the CYP2D6 substrate should be considered.[1]

In a clinical pharmacokinetic interaction study, the pretreatment of healthy volunteers with a strong CYP3A4 inducer (rifampicin) 600 mg daily for 6 days followed by a single dose of abiraterone acetate 1000 mg resulted in a 55% decrease in the mean plasma AUC_{∞} of abiraterone acetate.[1] Thus, strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with abiraterone acetate should be avoided, or used with careful evaluation of clinical efficacy.[1]

In healthy volunteers, concurrent therapy with abiraterone acetate and ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone acetate.[1]

EXPERT COMMENTARY ON THE THERAPEUTIC EFFICACY OF ABIRATERONE ACETATE IN THE TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

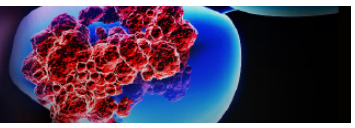
The efficacy of oral abiraterone acetate in combination with oral prednisone has been investigated in two phase III trials involving men with mCRPC who had either previously received docetaxel[2,15-19] or had not previously received chemotherapy.[3] The results of these trials are discussed below.

Abiraterone and increased survival in metastatic prostate cancer[2]

Summary: In this investigation into the use of abiraterone acetate in the post-chemotherapy setting, this phase III trial (COU-AA-301) randomised 1195 patients with mCRPC who had previously received docetaxel to receive 5 mg of prednisone twice daily with either 1000 mg of abiraterone acetate (n=797) or placebo (n=398). The primary end point was overall survival. The secondary end points included time to PSA progression (elevation in the PSA level according to pre-specified criteria), radiographic progression-free survival (rPFS), and the PSA response rate. The median duration of treatment was 8 months in the group that received abiraterone acetate plus prednisone and 4 months in the group that received placebo plus prednisone.

After a median follow-up of 12.8 months, overall survival was significantly prolonged in the abiraterone acetate plus prednisone group compared with the prednisone-only group (14.8 months vs 10.9 months; hazard ratio [HR] 0.65; 95% CI, 0.54 to 0.77; p<0.001).

All secondary end points, including time to PSA progression (10.2 vs 6.6 months; p<0.001), median PFS on the basis of radiographic evidence (5.6 months vs 3.6 months; p<0.001), PSA response rate (29.1% vs 5.5%; p<0.001) and objective response (as according to the Response Evaluation Criteria In Solid Tumors, RECIST; 14.0% vs 2.8%; p<0.001) favoured the combination treatment group. Mineralocorticoid-related adverse events, including fluid retention, hypertension, and hypokalaemia, were more frequently reported with abiraterone acetate plus prednisone than with prednisone alone.



Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study[15]

Summary: This final overall survival analysis of study COU-AA-301 confirms a continued trend in prolongation of life in patients with mCRPC treated with abiraterone acetate plus prednisone compared with those treated with prednisone alone. Moreover, no new safety concerns were identified with increased follow-up.

At a median 20.2 months of follow-up, median overall survival was significantly prolonged with abiraterone acetate compared with prednisone monotherapy (15.8 months vs 11.2 months; HR 0.74; 95% CI, 0.64 to 0.86; p<0.0001). The secondary end points of median time to PSA progression (8.5 months vs 6.6 months; HR 0.63; 95% CI, 0.52 to 0.78; p<0.0001), median rPFS (5.6 months vs 3.6 months; HR 0.66; p<0.0001), and proportion of patients who had a PSA response (29.5% vs 5.5%; p<0.0001) were all improved in the abiraterone acetate group compared with the prednisone-only group. The most common grade 3/4 adverse events were fatigue (9% of patients in the abiraterone acetate group vs 10% of the prednisone-only group), anaemia (8% vs 8%, respectively), back pain (7% vs 10%, respectively) and bone pain (6% vs 8%, respectively).

Comment: This study is important in many aspects. It is the first large international randomised trial to demonstrate survival benefit with a hormonal agent in patients who have cancer progression after docetaxel chemotherapy. It confirms that targeting the androgen signalling pathway remains valid and beneficial even in men who have hormone-resistant/androgen-independent disease (old terms for CRPC). It builds on earlier studies demonstrating that inhibiting steroidogenic pathways can suppress both peripheral and intratumoural androgen levels, resulting in cancer shrinkage, control and clinical benefit.

The patients were all castration-resistant, nearly a third had cancer progression after two lines of chemotherapy, 90% presented with bone mets and more than 40% had nodal disease. These are unwell heavily pretreated patients with real cancer morbidity.

The trial clearly demonstrates improvement in all disease-related indices from overall survival, PSA 50% response, PSA progression-free survival and a novel outcome measure of radiographic progression-free survival. Multivariable analysis showed improvement in survival in all subgroups, although some did not meet statistical significance due to small numbers.

Adverse events attributable to abiraterone that are of reasonable significance and severity are all ≤5%. These are generally nausea, GI symptoms such as diarrhoea, constipation, anorexia, hypertension, hypokalaemia, abnormal LFT and oedema. The clinician should be mindful of chronic steroid dosing implications.

Subsequent separate publications from the same COU-AA-301 trial analysed clinically relevant outcomes such as efficacy and safety in the elderly (≥75 years), improvement in pain control and skeletal-related events. These data (reviewed in the following studies) have confirmed a clinical benefit that is relevant in clinical practice.

Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy[16]

Summary: This post-hoc analysis of data from the COU-AA-301 trial confirms that abiraterone acetate improves overall survival and is well tolerated in elderly patients with mCRPC after docetaxel-based chemotherapy. According to these findings, abiraterone acetate is an important treatment option for older men who may not be able to tolerate alternative therapies that are associated with greater toxicity.

This analysis examined the efficacy and safety of abiraterone acetate plus prednisone versus prednisone alone in subgroups of elderly (aged ≥75 years) (n=331) and younger patients (<75 years) (n=863).

Elderly patients in the abiraterone acetate plus prednisone arm experienced improvements in overall survival (median 15.6 months vs 9.3 months; HR 0.64; 95% CI, 0.478 to 0.853; p=0.0022), time to PSA progression (median 11 months vs 8.5 months; HR 0.76; 95% CI, 0.503 to 1.155; p=0.1995), and rPFS (median 6.6 months vs 5.4 months; HR 0.66; 95% CI, 0.506 to 0.859; p=0.0019) and a significantly higher PSA response rate (34% vs 8%; HR 4.15; 95% CI, 2.2 to 8.0; p≤0.0001), compared with elderly patients receiving prednisone alone.

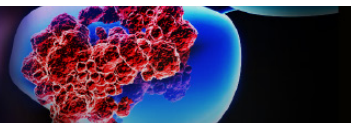
Study treatment was well tolerated by most patients in both age subgroups; dose reductions occurred in ≤3% of patients across treatment arms. Grade 3/4 adverse events occurred in 62% of elderly patients and in 60% of younger patients treated with abiraterone acetate plus prednisone. Hypertension and hypokalaemia were reported more often in the combination treatment arm than with prednisone alone, but the incidences were similar in both age subgroups and readily managed.

Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial[17]

Summary: In this investigation, abiraterone acetate plus prednisone favourably affected measures of disease-related symptoms (i.e., patient-reported pain palliation, delay in pain progression, and delayed time to skeletal-related events) in the COU-AA-301 trial, compared with treatment with prednisone alone.

Pain intensity and interference of pain with daily activities were assessed with the Brief Pain Inventory-Short Form (BPI-SF) questionnaire at baseline, day 15 of cycle 1, and day 1 of each treatment cycle thereafter until discontinuation. Clinically meaningful changes in pain intensity and interference with daily living were assessed with prospectively defined response criteria that incorporated analgesic use. Skeletal-related events were defined as pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. Pain palliation was assessed in patients who had clinically significant pain at baseline, whereas all other analyses were done in the overall intention-to-treat population.

Median follow-up was 20.2 months. Significantly more patients in the abiraterone acetate plus prednisone group reported palliation of pain (45.0% vs 28.8%; p=0.0005) and palliation of pain interference (60.1% vs 38.0%; p=0.0002) compared with those treated with prednisone only. Moreover, median times to palliation of both pain and pain interference, as well as the median duration of palliation of pain intensity, were significantly better with abiraterone acetate plus prednisone than with prednisone only. In the overall population, median time to occurrence of first skeletal-related event was significantly longer with abiraterone acetate and prednisone than with prednisone only.



Abiraterone in metastatic prostate cancer without previous chemotherapy[3]

Summary: To investigate the use of abiraterone acetate in the pre-chemotherapy setting, this randomised, double-blind, placebo-controlled phase III trial (COU-AA-302) was conducted to evaluate the effects of abiraterone acetate plus prednisone on rPFS, overall survival, increase in pain, and clinically relevant measures of disease progression in men with progressive mCRPC who had not received chemotherapy and in whom clinically significant cancer-related symptoms had not developed. The study assigned 1088 such patients to treatment with either abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily (n=546) or placebo plus prednisone 5 mg twice daily (n=542), until progression. The mean number of treatment cycles was 15 for abiraterone acetate and 9 for placebo. Fifty-seven percent of patients in the abiraterone acetate group versus 68% of those in the placebo group discontinued due to progression of disease.

Combination therapy with abiraterone acetate plus prednisone significantly prolonged median rPFS compared with prednisone alone (16.5 months vs 8.3 months; HR 0.53; 95% CI, 0.45 to 0.62; p<0.001). Over a median 22.2-month follow-up, abiraterone acetate plus prednisone was associated with an improvement in overall survival (median not reached vs 27.2 months for prednisone alone; HR 0.75; 95% CI, 0.61 to 0.93; p=0.01) but did not cross the efficacy boundary. Moreover, abiraterone acetate plus prednisone was significantly superior over prednisone alone with respect to time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression, and decline in performance status. Grade 3 or 4 mineralocorticoid-related adverse events and liver function abnormalities were more common with abiraterone plus prednisone than with prednisone alone.

The study authors have since pointed out that the safety profile in this study did not differ from the study reported above in previously-treated mCRPC, despite the longer duration of treatment in this study with abiraterone acetate plus prednisone.[18]

Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study[19]

Summary: The final, long-term follow-up data from the above-mentioned study confirm the survival benefit of abiraterone acetate in the treatment of chemotherapy-naïve patients with mCRPC, even after adjusting for crossover of 44% of placebo-treated patients to the abiraterone acetate arm.

After a median follow-up of 49.2 months, the final analysis of overall survival was performed after 741 deaths (96% of 773 expected deaths). Survival was significantly prolonged with abiraterone acetate plus prednisone compared with prednisone alone (median 34.7 months vs 30.3 months; HR 0.81; 95% CI, 0.70 to 0.93; p=0.0033). The survival treatment effect was consistent across all prespecified subgroups. In analyses that adjusted for the crossover effect, the risk of death remained lower in the abiraterone acetate group than in the placebo group and the decrease was greater than without the adjustment (HR 0.74; 95% CI, 0.60 to 0.88).

In a multivariate analysis that accounted for variations in baseline prognostic factors, the risk of death was significantly decreased by treatment with abiraterone acetate plus prednisone compared with placebo plus prednisone (HR 0.79; 95% CI, 0.68 to 0.91; p=0.0013). Notably, baseline PSA, lactate dehydrogenase, alkaline phosphatase, haemoglobin, bone metastases, and age were all significant prognostic factors for overall survival, but Eastern Cooperative Oncology Group performance status (ECOG-PS) score was not. Patients who had a lower ECOG-PS (0 vs 1) at baseline, were asymptomatic at baseline or had bone metastases only, did better.

Adverse events at the time of the final analysis were similar for those previously reported for the second interim analysis, after nearly 27 months of additional follow-up. Adverse events of special interest reported at the final analysis, including events related to mineralocorticoid excess, were more commonly reported with abiraterone acetate treatment than with prednisone alone; the majority were of grade 1 or grade 2 intensity. Grade 3 or 4 adverse events of special interest reported in the abiraterone acetate group at the final analysis were similar to those reported at the second interim analysis. The most common adverse events in the final analysis resulting in death in the abiraterone acetate group were disease progression and general physical health deterioration as a sign of clinical progression (each event affected 3 patients). No treatment-related deaths occurred and no new safety indications were identified with longer treatment exposure to abiraterone acetate.

Comment: The success of targeting the androgen steroidogenic pathway logically led to the pre-chemotherapy study of mCRPC patients. This population is at worst only mildly symptomatic, which is an important aspect, as patients with higher pain scores tend to have greater disease burden and poorer prognosis/outcome response to therapy.

It is noteworthy that low-dose corticosteroid is associated with a response rate in just over a quarter of patients. No additional toxicities of concern were identified, but more mature percentages of adverse events seen (slightly higher now) underscore the importance of close monitoring of CYP17 inhibitor therapy. The trial was closed early due to improvement seen in overall survival, the Data Safety Monitoring Committee recommended that patients on placebo be given abiraterone. Despite a crossover rate of 44%, and the availability of subsequent therapies, overall survival was still observed. Clinical benefits across all subgroups were seen, including PRO (patient-reported outcomes) in favour of abiraterone for pain and quality of life scores. We now have an alternative treatment to docetaxel chemotherapy in mCRPC that is well tolerated.

This trial importantly contributes to defining rPFS as a valid surrogate endpoint in mCRPC research, as more agents become available for treatment.

This last paper presents the final analysis of an early-access protocol trial and provides real-world experience of using abiraterone acetate among patients with mCRPC progressing after chemotherapy.[20]

Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial[20]

Summary: This multicentre, open-label, early-access protocol trial reports no new safety signals or unexpected adverse events with abiraterone acetate in men with mCRPC who progressed after chemotherapy.

This protocol trial was initiated after completion of COU-AA-301 to enable worldwide preapproval access to abiraterone acetate for the treatment of patients with mCRPC progressing after chemotherapy. A total of 2314 such patients across 23 countries were enrolled into the early-access protocol trial, between 17 November 2010 and 30 September 2013.

Median follow-up was 5.7 months. Grade 3 or 4 treatment-related adverse events were recorded in nearly half of all patients (41%), while grade 3 or 4 serious adverse events were recorded in a quarter (25%). Grade 3 and 4 adverse events of special interest included hepatotoxicity (8%), hypertension (4%), cardiac disorders (2%), osteoporosis (1%), hypokalaemia (1%), and fluid retention or oedema (1%). Of the 172 (7%) patients who discontinued the study because of adverse events, 64 (3%) were drug-related (as assessed by the investigator) and 171 (7%) patients died. The funder judged 85 (4%) deaths to be caused by disease progression, 72 (3%) due to an unrelated adverse experience, and 14 (<1%) as caused by unknown reasons. Of the 86 deaths deemed unrelated to disease progression, 18 (<1%) were attributed to a drug-related adverse event, as assessed by the investigator. At clinical cut-off, median time to PSA progression was 8.5 months and median time to clinical progression was 12.7 months.

Comment: The "real world" experience of a novel drug/drug group is important, as the selection of well patients within a clinical trial may not be generalisable to the population treated in the clinic. The EAP (expanded access program) here was conducted in some countries not included in the 301 trial. Australia contributed to 13% of patients. Toxic effects frequency and grades were roughly similar, which is reassuring. The median duration of treatment was about 5 months, shorter than the 7.5 months reported in the trial, raising suspicion of under-reporting of toxicity, considering the median time to clinical disease progression (a meaningful pragmatic outcome) was nearly 13 months.

We also know that the proportion of patients stopping treatment due to drug toxicity is between 7 and 13% (from the 301 study and the EAP).

Overall, this affirms that benefit and toxicity of abiraterone post-chemotherapy is comparable to the 301 trial report.

CONCLUDING REMARKS AND TAKE-HOME MESSAGES

Abiraterone defined an era of definitive evidence demonstrating that targeting the androgen signalling axis pathway is important in the treatment of mCRPC. Two large trials provide irrefutable evidence for survival and clinical benefit in the treatment of mCRPC, and with the arbitrary definition of pre- or post-chemotherapy now becoming less clear.

In the treatment of mCRPC, where overall survival used to be around 12 months, the steady increase to around 36 months now with sequential therapies is a huge leap forward. Several points are pertinent.

Since the advent of LHRH agonist and first-generation anti-androgens in the 1980s, then with docetaxel chemotherapy in 2004, there are now 5 FDA/EMA approved systemic agents for the treatment of mCRPC that improve survival. They include:

- Enzalutamide, a novel anti-androgen hormonal treatment, with proven efficacy and survival benefit in both the post- and pre-chemotherapy settings.
- Sipuleucel-T, an autologous vaccine based around the targeting of prostate acid phosphatase; this treatment is the first approved solid tumour vaccine.
- Cabazitaxel, a taxane chemotherapy effective after docetaxel failure.
- Radium-223 (Alpharadin), an alpha-particle emitting therapeutic radionuclide targeting bone metastases.

The oral hormonal therapies of abiraterone and enzalutamide provide an added level of convenience in administration. Abiraterone is now funded by PHARMAC under Special Authority, and enzalutamide registration is pending.

The challenge is to define which agent to utilise, as there is no defined biomarker selecting an agent to use or not to use. Furthermore, none have been compared with one another, although resistance to one agent probably predicts a more resistant phenotype. Considered approach and utilisation of these drugs by an experienced clinician is expected to improve outcome in these patients.

Patients benefit more when treated early, even in the asymptomatic stage. This is ever more important, not just with multiple systemic agents but also with multiple modalities (judicious interdigitation of palliative radiotherapy to symptomatic sites). Closer monitoring, appropriate use of imaging modalities and earlier involvement of the medical oncologist in a multidisciplinary approach will improve outcomes for our patients.

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