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Abiraterone acetate: a hat trick of clinical benefits

Michael T Schweizer and Emmanuel S Antonarakis

Prostate Cancer Research Program, Sidney Kimmel, Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21287, USA

Emmanuel S Antonarakis: eanton1@jhmi.edu

A substantial proportion of men with advanced prostate cancer develop bone metastases, which can lead to pronounced morbidity as a result of bone pain and skeletal-related events.¹ Many newer drugs for metastatic castration-resistant prostate cancer, including abiraterone acetate, have a broad range of efficacy, which manifests as prolonged survival and improved quality of life.

In *The Lancet Oncology*, Christopher Logothetis and colleagues² report the outcomes related to pain and skeletal-related events from COU-AA-301, the placebo-controlled phase 3 trial that led the US Food and Drug Administration to approve abiraterone acetate for use in the postchemotherapy setting. The authors report that, in men with clinically significant pain scores at baseline, abiraterone acetate and prednisone led to palliation of pain in 157 of 349 patients (45.0%) compared with 47 of 163 (28.8%) given placebo and prednisone ($p=0.0005$); pain palliation was also achieved more quickly in patients given abiraterone acetate and prednisone (5.6 months vs 13.7 months, $p=0.0018$). A delay of 4.7 months in median time to first skeletal-related event was also noted in the abiraterone acetate plus prednisone group compared with the prednisone only group (HR 0.615, 95% CI 0.478–0.791; $p=0.0001$). These data show abiraterone acetate's therapeutic versatility.

Although it seems intuitive that drugs leading to improved overall survival in men with metastatic castration-resistant prostate cancer would also lead to improvements in pain and functionality, this has not always been the case. The most apparent example of a treatment with discordant survival and palliative effects is the autologous immunotherapy product sipuleucel-T.³ A range of new drugs that improve survival as well as quality of life are now available—including the chemotherapeutics docetaxel and cabazitaxel, the radiopharmaceutical radium-223, the novel androgen-signalling inhibitor enzalutamide, and abiraterone acetate^{2,4–8}—and thus the bar has been raised in terms of choosing which drugs to prescribe. Survival alone might not be enough.

Conversely, some drugs show clear palliative benefits but do not affect overall survival—eg, the osteoclast inhibitors denosumab and zoledronate, both of which help to prevent skeletal-related events (zoledronate also improves pain scores).^{9,10} It should be noted that, although the phase 3 trial comparing denosumab with zoledronate was not powered to specifically

Correspondence to: Emmanuel S Antonarakis, eanton1@jhmi.edu.

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assess pain outcomes, pain events occurred at similar frequencies in both groups. On the basis of Logothetis and colleagues' study, abiraterone acetate can join radium-223 and enzalutamide in improving both overall survival and skeletal-related events.^{2,6–8}

Logothetis and colleagues' study has several limitations. First, previous bisphosphonate use—a potentially confounding issue—was not controlled for. A multivariable analysis adjusting for previous or ongoing bisphosphonate use would be helpful to establish whether osteoclast inhibition could have accounted for some of the improvements in pain scores and skeletal-related events noted in the abiraterone acetate group. The median pain score of patients enrolled in COU-AA-301 was 3/10, with clinically significant pain defined as 4/10 or greater. Although this point might seem trivial (because only those with significant pain were included in the analysis of pain-related outcomes), it is not clear what the baseline characteristics were for patients who experienced a palliative benefit. We do not doubt that abiraterone acetate provides a palliative benefit and delays skeletal-related events. However, we would caution against a palliation and prevention strategy for skeletal-related events that relies exclusively on the drug.

Although COU-AA-301 was not powered specifically to detect improvements in pain scores, several clinical trials have been designed with pain palliation endpoints in mind, such as a phase 3 study comparing cabozantinib with mitoxantrone hydrochloride in men with docetaxel-refractory metastatic castration-resistant prostate cancer (NCT01522443) and another assessing the anti-clusterin oligonucleotide custirsen plus a taxane in men with docetaxel-refractory disease (NCT01083615). Both trials have used pain responses as their primary endpoints—a clear acknowledgment that palliation probably deserves a more prominent role in future trial design.

In summary, mounting evidence suggests that abiraterone acetate not only extends survival in patients with metastatic castration-resistant prostate cancer, but also improves pain and delays skeletal-related events, providing a hat trick of clinical benefits—ie, improving how long patients survive, feel, and function. The time has come for trials to be designed not only to establish survival improvements, but also to define the palliative role that newer drugs might have in the treatment of advanced prostate cancer.

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