

of the hypothalamic-pituitary-testicular (HPT) axis in association with aging as well as the finding that a number of largely independent risk factors contribute to the hormonal alterations. Since these risk factors are potentially modifiable, we should look at strategies to maintain the hormonal milieu in the aging population. These strategies should translate into improved endothelial, bone, and sexual health, among other benefits.

Conflicts of interest: The author has nothing to disclose.

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Re: Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms That Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven

Attard G, Reid AH, Yap TA, Raynaud F, Dowsett M, Settattree S, Barrett M, Parker C, Martins V, Folkard E, Clark J, Cooper CS, Kaye SB, Dearnaley D, Lee G, de Bono JS

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Expert's summary:

Evidence is increasing that the androgen receptor is still playing a significant role in castration-resistant prostate cancer. In order to further decrease tissue androgen levels, a low-molecular-weight inhibitor of cytochrome P (CYP) 17 was tested in a phase 1 clinical trial. CYP 17 is a key enzyme in the synthesis of androgens, particularly in the synthesis of precursors for androgens and estrogens. In this phase 1 study, 21 chemotherapy-naïve patients were included. The dose of the compound abiraterone acetate was increased in five steps from 500 mg to 2000 mg daily orally. The drug was well tolerated. The anticipated toxicities due to secondary mineralocorticoid excess could be managed with a mineralocorticoid-receptor antagonist. There was a marked decline of prostate-specific antigen (PSA) in 20 out of 21 patients, with 57% showing PSA declines of >50%. Also, radiological regression and normalization of LD and improved symptoms with a reduction in analgesic use were documented. The data provide a solid basis for further phase 2 testing.

Expert's comments:

The first indications that the androgen receptor plays an important role in endocrine therapy-resistant prostate cancer were presented in 1991 by van der Kwast et al [1]. This finding has subsequently been reproduced by several other teams [2,3]. Further-

more, in patients with castration-resistant prostate cancer, significant levels of dihydrotestosterone (DHT) are found in the cancer tissue. This observation from the mid-1980s was reconfirmed by recent studies [4,5]. Thus, there is a strong rational basis for therapies based on interference with androgen synthesis. Abiraterone acetate is the first CYP17 inhibitor that showed remarkable clinical effects in a phase 1 study. The anticipated side effects can be managed. The trial greatly benefited from our thorough understanding of androgen synthesis. The CYP17 inhibition inevitably results in increases in mineralocorticoids, and thus one can anticipate hypokalemia, hypertension, fluid overload, and suppression of renin. However, by administering a mineralocorticoid receptor antagonist, these effects could be managed well. The pharmacodynamic profiles were satisfactory, although it should be mentioned that a high-fat meal results in faster uptake of the compound. Sustained plasma concentrations of approximately 0.1 nmol/L were achieved.

The strong serum PSA reduction in this patient group is remarkable. Long-term PSA decreases of ≥50% were observed. From a scientific perspective, it was interesting that even though the group was small, the authors decided to evaluate *TMPRSS2-ETS* gene fusion status [6]. The *TMPRSS2-ETS* genes are driven by the androgen receptor and could be an important mediator of growth in castration-resistant prostate cancer. In 18 patients, the *TMPRSS2-ERG* gene status was determined, and 6 patients (33%) turned out to be gene fusion-positive. This is in agreement with two other studies that have looked at *TMPRSS2-ERG* gene fusions in castration-resistant prostate cancer [7,8].

Five out of six (83%) patients had >50% PSA decline, which is almost 30% more than the overall group. Albeit a small study cohort, this suggests that gene fusion status may be indicative for response to abiraterone acetate.

This study is based on a well-validated working hypothesis; that is, the fact that the androgen receptor still plays a significant role in patients that are progressive under the currently available endocrine therapies (now commonly called castration-resistant prostate cancer). The PSA and clinical responses are remarkable. I think the scientific community will follow the development of this exciting new drug with great interest.

Conflicts of interest: The author has nothing to disclose.

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Re: Utilization and Outcomes of Minimally Invasive Radical Prostatectomy

Hu JC, Wang Q, Pashos CL, Lipsitz SR, Keating NL

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Experts' summary:

In an attempt to demonstrate improved outcomes of minimally invasive radical prostatectomy (MIRP) compared to open radical prostatectomy, Hu et al analysed a 5% random sample of Medicare beneficiaries operated between 2003 and 2005. Based on this cohort of 2702 men aged ≥ 65 yr, significant advantages for MIRP were observed with regard to length of hospital stay (average: -2.99 d) and overall perioperative complication rate (29.8% vs 36.4%; particularly cardiac, respiratory, wound/bleeding, genitourinary, and miscellaneous medical complications). Patients who underwent MIRP, however, had a significantly greater number of anastomotic strictures (odds ratio: 1.4) and required more salvage therapies in the form of radiotherapy and injectable hormone therapy up to 6 mo after surgery (odds ratio: 3.67).

Experts' comments:

It was mainly the pioneering work of European urologists that resulted in the invention of laparoscopic radical prostatectomy (LRP). Based on pre-

sumed advantages, laparoscopic and, more recently, robotic-assisted laparoscopic prostatectomy have gained widespread use. Indeed, several studies demonstrate less blood loss, lower perioperative transfusion rates, less pain (based on analgesic use), shorter hospital stay, and faster convalescence after MIRP compared to open radical prostatectomy.

In order to further substantiate the advantages of MIRP, Hu et al studied a representative cohort of randomly selected Medicare beneficiaries. Due to case selection based on procedural codes, it was impossible to differentiate between laparoscopic and robot-assisted prostatectomy; however, in 2003–2005, the majority of MIRP cases presumably underwent pure laparoscopy. In line with other studies, Hu et al confirmed a shorter hospital stay and fewer perioperative complications after MIRP. In particular, medical complications such as cardiac and respiratory events appeared to be significantly decreased with a minimally invasive approach, underlining its importance! In sharp contrast, MIRP resulted in a greater number of anastomotic strictures and an unacceptable rate of salvage procedures at 27.8%. Taking into account the long learning curve of LRP, with all of the disadvantages for the patients, it is striking that even after surgery by a “high-volume” MIRP surgeon, the requirement