

Expert's comments:

The development of a second-generation hormone therapeutic offers new perspectives for the treatment of CRPC, both prior to and subsequent to chemotherapy.

Abiraterone acetate is a potent, selective small molecule that irreversibly inhibits CYP17, an enzyme that catalyses two key steps in androgen biosynthesis [2]. Recent data [3] showed prostate-specific antigen (PSA) declines of 50% in about 60% of chemotherapy-naïve patients and in about 40% of postchemotherapy patients. The median time to progression in the two groups was 8 mo and 5.5 mo, respectively. Some data [4] suggest that cancers with a *TMPRSS2:ERG* fusion may represent a subpopulation that is enriched for hormone-dependent CRPC, but these cases do not account for all of the clinical responses to abiraterone acetate.

MDV3100 derives from a new family (diarylthiohydantoin). It has been selected from a panel of nearly 200 products [5]. MDV3100 binds androgen receptors with an eight-fold higher affinity than bicalutamide, reduces the efficiency of its nuclear translocation, and impairs both DNA binding to androgen response elements and the recruitment of coactivators. This third-generation antiandrogen is characterized by the lack of agonist conversion when androgen receptors are overexpressed. The latest update at the 2009 American Society of Clinical Oncology meeting reported safety data on the first 114 patients who were enrolled in the phase 1/2 trial. The treatment was generally well tolerated, with a dose-limiting toxic effect of fatigue. After 12 wk of treatment, 36 of 65 (55%) chemotherapy-naïve patients and 27 of 75 (36%) postchemotherapy patients attained a PSA decline of >50% from baseline. These very promising clinical data must be confirmed in phase 3 registration trials. The accrual of a phase 3 trial

evaluating abiraterone acetate after chemotherapy in metastatic CRPC is already completed (1180 patients).

These drugs should become the new standard of care in the near future. The two major challenges for these new drugs in the next few years will be the selection of biomarkers that could predict clinical benefit and their use at initial stages, particularly in hormone-therapy-naïve disease.

Conflicts of interest: The author has nothing to disclose.

References

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Re: Maternal Smoking, Alcohol, and Coffee Use During Pregnancy and Son's Risk of Testicular Cancer

Mongraw-Chaffin ML, Cohn BA, Anglemeyer AT, Cohen RD, Christianson RE

Alcohol 2009;43:241–5

Expert's summary:

The Child Health and Development Studies are a prospective 40-yr follow-up of 20 530 pregnancies between 1959 and 1967. Twenty testicular cancer (TC) cases diagnosed through 2003 with an available maternal interview from early in pregnancy were each matched to three controls. Mothers of sons with TC were more likely to drink alcohol (odds ratio [OR]: 3.2) and show lower testosterone levels during pregnancy compared to controls. They were less likely to drink coffee (OR: 0.19). Maternal smoking had no influence on TC risk. These prospective data provide more information about the role of lifestyle environmental exposures on the development of TC.

Expert's comments:

As the prevalence of TC and cryptorchidism has increased and as semen quality has decreased over time, scientific

focus has been directed to environmental hormone-disrupting chemicals and lifestyle influences. Lifestyle alcohol consumption seems to be an additional cause leading to hormonal disorders during pregnancy, especially to lower testosterone levels, which were found in this study.

Disturbed gonadal development in the embryo may result in male reproductive disorders (cryptorchidism, hypospadias, infertility, and TC), representing the testicular dysgenesis syndrome (TDS) [1]. Other causes of TDS may be environmental hormone disrupters like polychlorinated pesticides, polybrominated flame retardants, and prenatal exposure to phthalates (plasticizers), all negatively correlated to testosterone levels [2]. High estradiol (OR: 32) and androstenedione (OR: 4.1) levels were associated with an increased risk for TC, whereas high levels of dehydroepiandrosterone sulfate decreased the risk (OR: 0.18) [3]. Although it was a possible risk factor for cryptorchidism [2], smoking during pregnancy did not increase the risk for TC in the offspring, as shown by a meta-analysis of seven epidemiologic studies (2149 cases) [4].

Decreasing maternal testosterone during pregnancy as well as lower testosterone levels in the general population of young men seem to be the main reasons for the higher

incidence of TC today. Increasing awareness of TC, together with the fear of being affected by this disease, underscores the need to define risk groups with the use of databases like that of the US National Institute of Child Health and Human Development. Knowledge of the facts may help optimize the efforts of urologists in promoting regular self-examination of the testes. Pregnant women should be informed about the possible risks of alcohol consumption and contact with pesticides, flame retardants, and plasticizers.

Conflicts of interest: The author has nothing to disclose.

Re: XMRV Is Present in Malignant Prostate Epithelium and Is Associated With Prostate Cancer, Especially High-grade Tumors

Schlager R, Choe DJ, Brown KR., Thaker HM, Singh IR

Proc Natl Acad Sci U S A 2009;160:16351–6

Experts' summary:

Xenotropic murine leukemia virus-related virus (XMRV) was recently identified in prostate cancer (PCa) tissue. Schlager and colleagues provide morphologic and molecular evidence that XMRV is a gammaretrovirus, a group of viruses known to cause cancers in many species. Expression of XMRV was studied with quantitative polymerase chain reaction (PCR) and immunohistochemistry, two sensitive and specific means of determining the expression of this virus in patients with and without PCa.

The most notable finding was the high presence of XMRV viral protein in prostates positive for cancer (23%) compared to benign prostates (4%). The expression of the virus in PCa specimens was unrelated to the presence the RNASEL R462Q polymorphism, which was previously suggested to be a prerequisite for infection with this virus [1]. Another important outcome examined was the association between the presence of XMRV and PCa Gleason grade, with higher grade cancers more likely to express XMRV.

Experts' comments:

This study is the first to show that XMRV is found almost exclusively in patients with PCa and particularly in those with higher grade disease. Unlike previous reports showing that XMRV was more likely positive in those with the homozygous RNASEL R462Q variant, this study revealed no association with this polymorphism. Measurements of both viral protein and viral DNA support this conclusion and likely carry more sensitivity for virus detection than the

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prior reports, which only assessed viral RNA with reverse transcription PCR [1,2]. In short, all men are susceptible to XMRV and the subsequent potential PCa risk, not just the small portion of the population with the hereditary RNASEL R462Q variant.

These data provide compelling evidence for an association between XMRV infection and PCa. If a causal association can be proven, these findings would completely alter our understanding of prostatic carcinogenesis and would raise the possibility of PCa being linked to a sexually transmitted disease. Translational roles for XMRV testing may be relevant for discerning men who are at increased PCa risk to plan for chemoprevention. Additionally, we may be able to identify men who may not benefit from active surveillance. These possibilities are very exciting!

Conflicts of interest: The authors have nothing to disclose.

References

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