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Commentary

Grade-dependent Response to Finasteride in Early Prostate Cancer

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Androgen deprivation therapy (ADT) of androgen-dependent prostate cancer (PCa), which is still the gold standard treatment, was based Huggins and Hodges' 1941 finding that the growth of PCa cells requires the androgen, testosterone (Rick & Schally, 2015). In addition, an increasing body of evidence has revealed that the development and progression of androgen-dependent PCa to castration-resistant prostate cancer (CRPC) have an intimate association with the androgen-androgen receptor axis (AR axis) (Knudsen & Scher, 2009). The application of AR axis drugs, such as the 5 α -reductase inhibitors (5ARI), finasteride and dutasteride, which decrease levels of dihydrotestosterone (DHT) in order to prevent development or progression of PCa, remains to be extensively discussed and is controversial (Kosaka et al., 2014). The concept is driven by the results of two large, randomized, placebo-controlled trials: the Prostate Cancer Prevention Trial (PCPT) with finasteride (Thompson et al., 2003) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial (Andriole et al., 2010). In the PCPT, finasteride significantly reduced the overall risk of prostate cancer but cancers with high Gleason scores (7–10) were found in 6.4% of the tumors in the finasteride group, compared with only 5.1% of those being found in the placebo group.

In a manner analogous to the PCPT trial, the REDUCE trial reported an overall reduction in the number of PCa patients (with a low Gleason score of 5–6) in those receiving dutasteride versus those given a placebo (19.9% and 25.1%, respectively); similarly, tumors with a high Gleason score (8–10) were more frequent in the dutasteride-treated group than in the placebo group. In the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) trial, dutasteride was associated with a 38% decrease in the cancer detection rate on repeat biopsy at year 3 in men with low-grade Gleason score (5–6) prostate cancer undergoing active surveillance and who received three years of treatment with dutasteride or placebo (Fleshner et al., 2012).

Because of concerns regarding the possible induction of *de novo* aggressive PCa, the US Food and Drug Administration did not grant approval of 5ARIs for the chemoprevention of PCa in December 2010 (Theoret et al., 2011). However, it is still unclear whether the observed increase in high-grade CaP in these trials was real or artifact (Lucia et al., 2007). These observations cannot be fully explained from a purely mechanistic point of view. Therefore, further basic and clinical investigations are necessary (Kosaka et al., 2014).

In this issue of *EBioMedicine*, Kim et al. seek to improve biologic understanding of the grade-specific effects of the 5ARI, finasteride, by studying 183 men with localized prostate cancer, who were randomized to receive 5 mg of finasteride or placebo daily for 4 to 6 weeks pre-prostatectomy (Kim et al., 2016). In fact, this is one of the few studies done in early prostate cancer to investigate the time it takes for changes in gene expression to occur following finasteride therapy. The primary end point was to compare the frequency of expression of a predefined high-grade molecular signature (ER β , UBE2C, SRD5A2, and VEGF) differentiating high- and low-grade tumors in the Gleason grade (GG) 3 areas of finasteride-exposed tumors with those of placebo-exposed tumors, adjusted for Gleason score (GS) at prostatectomy. Secondary endpoints included assessment of androgen receptor (AR) levels, Ki-67, and cleaved caspase 3 to estimate the effects of finasteride on the expression of its downstream targets, cell proliferation, and apoptosis, respectively. Unfortunately, the primary endpoint could not be assessed as the predetermined molecular signature was not able to distinguish GG3 from GG4 areas in the placebo group.

However, expression of AR was significantly lower in the GG4 areas of the finasteride group compared to those of the placebo group (Kim et

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al., 2016). The authors claim that this finding is in accord with an emerging concept that reduced androgens in prostate tissues may, over time, lead to de-repression of AR expression, which, in turn, deregulates AR function and downstream de-repression of the AR target genes normally suppressed by androgens (Kim et al., 2016). Within the finasteride group, AR expression was also lower in GG4 than in GG3 areas, but not significantly.

Expression of the apoptosis marker, cleaved caspase 3, in GG3 and GG4 tumor areas was significantly increased after short-term exposure to finasteride, consistent with preventive efficacy, as shown in the PCPT, and was lower in GG4 than in GG3 areas within both treatment and placebo groups (Kim et al., 2016). In the literature, conflicting findings on the influence of 5ARIs have been reported, nonetheless, it seems that the molecular effects of 5ARIs depend on the exposure duration.

One major limitation of this trial is the short period over which the study was conducted: molecular alterations in tumors exposed to finasteride may occur over a longer period of time than 4–6 weeks. Another possible explanation is that the study was underpowered: the original projections of 100 patients for each group may have been inadequate. In addition, the evaluation of tumor samples was restricted to the peripheral zone and to samples with GG patterns primarily presenting poorly formed and fused glands. It is not known what changes occur in tumors of transition zone origin or other GG4 patterns.

In summary, this overall well-designed trial by Kim et al. emphasizes the necessity for further investigation of time-based effects of finasteride on molecular changes and their basic and clinical importance. Confirmation and extension of these findings may result in a valuable test

allowing the identification of finasteride-responsive tumors in order to provide personalized care and/or in improved estimates of the risk of progression of the individual's disease.

Disclosure

The authors declared no conflicts of interest relevant to this manuscript.

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