EDITORIAL COMMENT

The idea of intermittent hormonal therapy for recurrent and/or metastatic prostate cancer is appealing due to its presumed benefits of decreased cost, better quality of life and prolonged androgen sensitivity, although the latter was not substantially proven so far.

Recently, the concept of further delay of disease progression and prolongation of the off-treatment period (OTP) by additional pharmacological intervention has been introduced with a certain degree of effectiveness as has been suggested by a retrospective study (Reference 9 in the manuscript). Evidence suggested that finasteride doubles the duration of time off-hormonal therapy and AIPC was not increased by finasteride after almost 9 years of observation.[1]

Although, the kinetics of serum testosterone normalization after limited hormonal manipulation appears to be important in determination of OTP, entire process appears to be more complicated with the reported evidence that castrate resistant prostate cancer contain sufficient levels of testosterone and dihydrotestosterone (DHT) for AR transactivation as well as express all necessary enzymes for de novo DHT synthesis, and capable of intratumoral conversion of precursors to DHT alongside the usage of progesterone to synthesize DHT via steroidogenic pathways.[2]

Thus, interference with intracellular conversion of T to DHT may provide additional interim control of disease, as indicated by the results of the current study. Treatment by finasteride resulted in a decrease of PSA velocity and extended the PSA doubling time in all patients regardless of cycle evaluated. The mean PSA doubling time without finasteride was 7.7 weeks which was increased to a mean of 45.1 weeks with the addition of finasteride, which translates to a 6-fold increase. Yet the underlying molecular mechanisms are still questionable and actual role of 5-alpha reductase iso-enzymes (type 1 and 2) remains to be identified. A recent study indicated increased levels of 5 alpha-reductase type 1 and 2 in localized high grade prostate cancer compared to low grade tumors,[3] indicating a grade dependent differential expression of these iso-enzymes. Levels of 5 alpha-reductase type 1 were also higher in benign tissue adjacent to cancer than in benign prostatic hyperplasia. These results raise the possibility that increased 5 alpha-reductase type 1 in localized high grade cancers may contribute to the decreased effectiveness of the type 2 selective inhibitors, which may also in part explain the so called "pseudo-resistance" observed in some cases in the current study. It is still questionable whether dual inhibitors like dutasteride would be more effective in terms of achieving a longer OTP in this setting. Hopefully, optimal selection and timing of agents will be clarified by further investigations.

References

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