Platinum Priority


The Stage Is Set for Metformin

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1. Prologue

The “most fruitful basis of the discovery of a new drug is to start with an old drug,” said Sir James W. Black, 1988 Nobel laureate in medicine.

2. Act 1: Monotherapy

Metformin has been discussed as anticancer drug for some time [1]. The preclinical rationale for metformin use in prostate cancer (PCa) is discussed in the editorial [2]: direct actions of the drug on cancer cells and indirect effects related to changes on host hormone environment and metabolism. The former mechanism requires achievement of adequate drug concentrations in the prostate. The latter involves insulin and/or insulin growth factor 1 (IGF-1) signaling.

The IGF-1 receptor (IGF-1R) is a widely expressed receptor tyrosine kinase and activates the MAPK and PI3K/Akt signaling pathways [3]. Preoperative figitumumab, an IGF-1R antibody, has been reported to decrease IGF-1R and androgen receptor (AR) expression in prostatectomy samples and is associated with declines in prostate-specific antigen (PSA) levels [4]. In an earlier trial, the somatostatin analog octreotide acetate, which has been shown to reduce IGF-1 production, was assessed in patients with nonmetastatic castration-resistant PCa (CRPC). Circulating IGF-1 and insulin-like growth factor binding protein 3 were suppressed. However, in contrast to our study [5], the biochemical effect of octreotide was not mirrored in PSA or objective responses [6]. The paleness of the metformin effect in CRPC could be explained by the fact that PCa cells may be more dependent on IGF signaling prior to development of castration resistance, yet the story is more complex: Crosstalk between the AR and PI3K pathways has been shown preclinically, with PI3K pathway inhibition resulting in activation of AR through HER2/HER3 signaling and AR inhibition activating Akt [7].

3. Act 2: Combination treatment

Combination of metformin with abiraterone acetate or enzalutamide, as proposed in the editorial [2], is a plausible and attractive next step. The mechanisms leading to resistance against abiraterone are not, as yet, completely understood. Resistant tumor cells probably develop escape mechanisms with activation of pathways independent of...
androgens, for example, growth factor receptor pathways such as PI3K/Akt/mTOR [8]. Combined blockade of the androgen pathway and the mammalian target of rapamycin (mTOR) pathway was shown to restore sensitivity to antiandrogen therapy in a xenograft model [9]. Synergism of bicalutamide and metformin has been described in PCa cell lines [10], and this may also be true for the combination of enzalutamide and metformin. It is noteworthy that insulin, which is suppressed by metformin, reduces local androgen production by PCa cells [11].

4. Act 3: Potential predictors

Three transporters are known to be involved in metformin transport in humans: organic cation transporter 1 (OCT1), organic cation transporter 2, and multidrug and toxin extrusion 1 (MATE1). We will evaluate the correlation of predefined mutations within OCT1 and MATE1 and PSA response at 12 wk, time on treatment, and metabolic end points. However, due to the small sample size, further investigations will be needed, in search of other predictive markers.

5. Epilogue

Despite the lack of commercial interest in developing metformin, due to its generic status, large cooperative groups will hopefully continue exploring metformin to determine whether this drug can contribute to the treatment of PCa. The pharmaceutical industry may be motivated to explore more active, novel metformin analogs as well as combinations of metformin with newer drugs for PCa.

Conflicts of interest: The author has nothing to disclose.

References


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