Metformin and Androgen Deprivation Therapy Improves Prostate Cancer Survival

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Persistent prostate cancer cells after the initiation of androgen deprivation therapy (ADT) for advanced prostate cancer (PC) remains an opportunistic area of cancer management. Data suggests residual cells have a number of metabolic abnormalities that may synergistically targeted with Metformin, a commonly prescribed oral diabetic medicine. We hypothesize that metformin plus ADT may improve outcomes in men with advanced PC. Using the National Veterans Affairs databases, we identified all men diagnosed with PC between 2000-2008 that were treated with ADT and had follow-up through October of 2015. We excluded patients treated with ADT for ≤6 months or receiving ADT concurrently with localized radiation therapy. Three cohorts were identified including non-diabetics, diabetics on metformin, and diabetics not on metformin. Our primary outcome was overall survival (OS) and secondary outcomes included skeletal related events (SRE) and PC-specific survival.

The total cohort after exclusions consisted of 87,344 patients of which 53,893 (61%) were non-diabetics, 14,517 (17%) were diabetics on metformin, and 18,934 (22%) were diabetics not on metformin. Mean age was 75 ±11y (non-diabetics), 71 ±12 (diabetics on metformin), and 75 ±10 (diabetics not on metformin), p<0.001. The median OS was 7.1, 9.1 and 7.4 y respectively (p<0.001). Multivariable Cox proportional hazards analysis assessing for predictors of OS showed improved survival in diabetics on metformin (HR 0.77, 95% CI 0.74-0.81; p<0.001) vs. diabetics not on metformin (HR 0.99, 95% CI 0.95-1.03; p=0.5) with non-diabetics as referent group while controlling for age, co-morbidity, and Gleason score. Assessing for predictors of SRE revealed no association between metformin use (HR 0.99, 95% CI 0.92-1.07; p=0.8) and SRE. Lastly, PC-specific survival was improved in diabetics on metformin (HR 0.72, 95% CI 0.67-0.78; p<0.001) and to a lesser extent diabetics not on metformin (HR 0.87, 95% CI 0.81- 0.93; p<0.001) with non-diabetics as referent group.

In conclusion, metformin use in patients with advanced PC receiving ADT is associated with improved OS and cancer-specific survival. In vitro data suggests Metformin may target this 'therapeutic niche' of persistent cancer cells after ADT. Outcomes for PC patients receiving metformin and ADT should be further evaluated in a prospective clinical trial.

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