Metabolic Modulation at The Time of Androgen Deprivation Therapy Improves Prostate Cancer Survival in Patients

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Background: Persistent prostate cancer cells after the initiation of androgen deprivation therapy (ADT) for advanced prostate cancer (PC) remains an opportunistic area of cancer management. Our work suggests residual cancer cells after ADT have a number of metabolic abnormalities that might be synergistically targeted. The National Veterans Affairs databases is a warehouse containing clinicopathologic data and detailed drug prescription information. To test the interaction of agents that alter metabolic features in patients initiating ADT for advanced PC, we looked at prescription information for metformin, statins and celecoxib and evaluated their associations with PC outcomes.

Methods: Patients diagnosed with PC between 2000-2008, treated with ADT, and had follow-up through 2015 were included. We excluded patients treated with ADT for ≤6 months or those receiving ADT and radiation. Three cohorts were identified including non-diabetics, diabetics on metformin, and diabetics not on metformin and two groups (ADT +/- drug) were used to compare for celecoxib and statins. Our primary outcome was overall survival (OS) and secondary outcomes included skeletal related events (SRE) and PC-specific survival (PCSS).

Results: The total cohort after exclusions consisted of 87,344 patients. Examining metformin use, 53,893 (61%) were non-diabetics, 14,517 (17%) were diabetics on metformin and 18,934 (22%) were diabetics not on metformin. Metformin use strongly improved OS(HR 0.82,95% CI 0.78-0.86, P<0.001), SRE(HR 0.82,95% CI 0.72-0.93; p<0.01) and PCSS(HR 0.70,95% CI 0.64-0.77; P<0.01)). A dose-response relationship was observed regarding cumulative duration of metformin use ≥ 36 months was the most protective. For PC patients initiating ADT, 1,581 (2%) were on celecoxib and 85,763 (98%) were not. The celecoxib group had lower PSAs at both diagnosis (7.0 vs 8.7 ng/mL, P<0.001) and upon the initiation of ADT (6.2 vs 7.3 ng/mL, P=0.002) compared to no celecoxib. No improvement in OS, SRE or PCSS was noted with celecoxib use. In a third analysis, 53,360 patients took statins and 33,986 did not at the time of ADT initiation. Statin users were younger (median 73 vs. 76, p<0.001), had a higher Charlson Comorbidity Index (CCI) >3 (3.1% vs 2.5%, p<0.001) and more likely to have a high grade (Gleason score 8-10) cancer (12.3% vs. 10.9%, p<0.001). Regardless, statin use improved OS(HR 0.69, 95% CI 0.66-0.72; p<0.001), SRE(HR 0.64, 95%CI 0.57-0.73; p<0.001) and PCSS(HR 0.58, 95% CI 0.54-0.63; p<0.001).

Conclusions: We conclude that the use of statins or metformin at the time of initiation of ADT for advanced prostate cancer is associated with improved prostate cancer-specific and overall survival. These agents are inexpensive, well-tolerated medications that offer a promising adjunct to ADT, but require further prospective studies. Studies on the direct tumor effects in this susceptible metabolic niche generated after ADT are ongoing.

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