Is Dexamethasone a Better Partner for Abiraterone Than Prednisolone?

I read with great interest the article by Auchus et al. [1] in which they comprehensively reviewed the use of prednisone with abiraterone acetate in the treatment of metastatic castration-resistant prostate cancer (CRPC). Although prednisolone is the most commonly used corticosteroid with abiraterone in clinical trials and is the standard of care as recommended by current guidelines, two recent trials have shown better response rates and progression-free survival with dexamethasone compared with prednisolone. In the first trial, Lorente et al. [2] showed that durable prostate-specific antigen (PSA) responses might be achieved with a switch from prednisolone to dexamethasone (0.5 mg/day) in patients progressing on abiraterone. In patients with CRPC and progressive disease with abiraterone-prednisolone, 11 of 30 patients (39%) had confirmed $\geq 30\%$ PSA decline after switching to dexamethasone with median time to PSA progression of 11.7 weeks. These results are comparable with the response rate (41%) and duration (2.8 months) with enzalutamide after abiraterone in CRPC treatment [3].

The second trial is a randomized phase 2 trial that compared the efficacy of prednisolone (5 mg b.i.d.) and dexamethasone (0.5 mg/day) in chemotherapy-naïve patients with CRPC. In evaluable patients, the PSA response rates were 47% versus 24% for dexamethasone and prednisolone, respectively ($p = 0.05$). Median time to PSA progression was 9.7 months on dexamethasone versus 5.1 months on prednisolone (hazard ratio, 1.6; 95% confidence interval, 0.9–2.8). Among patients who crossed over at PSA progression on prednisolone, 37% had a confirmed PSA response to dexamethasone [4]. Pharmacokinetic and pharmacodynamic differences between dexamethasone and prednisolone might partially explain this phenomenon. The half-life of dexamethasone is longer, which may result in more effective suppression of adrenocorticotropic hormone and more proficient antitumoral activity. Second, abiraterone inhibits CYP 3A4, decreases the clearance, and further increases the half-life of dexamethasone, whereas prednisolone is usually not affected [5]. On the other hand, differences in the activity of synthetic glucocorticoids at the glucocorticoid receptor level might also cause alterations in efficacy [6].

In conclusion, dexamethasone may be a better partner for abiraterone compared with prednisolone. Upfront use of dexamethasone with abiraterone or a switch from prednisolone to dexamethasone at PSA progression might be feasible options and are currently being tested in larger trials (ClinicalTrials.gov ID NCT01867710, Abiraterone With Different Steroid Regimens for Side Effect Related to Mineralocorticoid Excess Prevention in Prostate Cancer Prior to Chemotherapy).

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REFERENCES

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