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Dexamethasone may be the most efficacious corticosteroid for use as monotherapy in castration-resistant prostate cancer

S L Holder[1,*], J Drabick[1], J Zhu[2], and M Joshi[1]

[1]Division of Hematology/Oncology; Department of Internal Medicine; Penn State Milton S. Hershey Cancer Institute; Hershey, PA USA; [2]Department of Public Health Sciences; Penn State College of Medicine, Hershey, PA USA

Corticosteroids have been used in the therapy for castration-resistant prostate cancer (CRPC) for decades, both as monotherapy and in combination with additional agents. In this article the authors report the results of a phase II trial of dexamethasone versus prednisolone as monotherapy for CRPC. The study suggests improved PSA and radiographic response rates as well as improved time to PSA progression for dexamethasone over prednisolone therapy; however the differences only trend toward statistical significance. Nonetheless, in light of these data, when treating patients with corticosteroid monotherapy for CRPC it may be prudent to consider using daily dexamethasone over prednisone/prednisolone.

Keywords: castration-resistant prostate cancer, dexamethasone, prednisolone, prednisone

*Correspondence to: S L Holder; Email: sholder@hmc.psu.edu

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In the article entitled A Randomized Phase 2 Trial of Dexamethasone Versus Prednisolone in Castration Resistant Prostate Cancer, Venkitaraman et al., report the results of the first head to head trial of dexamethasone vs. prednisolone as monotherapy in castration-resistant prostate cancer (CRPC).[1] Corticosteroids have been known to have activity as monotherapy in CRPC for decades and currently remain an integral part of the therapeutic regimen, particularly in combination with cytotoxic chemotherapy or androgen synthesis inhibitors.

Although many previous studies used prednisone in CRPC, this study used prednisolone. It should be noted that prednisone is distinctly different from prednisolone, but is converted to prednisolone by hepatic enzymes. This study seeks to determine if there is a difference in efficacy between dexamethasone and prednisolone when used as monotherapy in CPRC. There are data suggesting improved efficacy of dexamethasone over prednisone in other disease types. For example, a meta-analysis evaluating the efficacy of dexamethasone versus prednisone in childhood acute lymphoblastic leukemia (ALL) found that dexamethasone was superior to prednisone for induction therapy.[2] In a recent report of results of the EORTC CLG 58951 study it was shown that dexamethasone was equivalent to prednisolone for induction therapy for ALL; however, dexamethasone was found to be superior to prednisolone for preventing central nervous system relapse.[3]

Here the authors conducted a phase II, single center, randomized, open-label study among chemotherapy naïve CRPC patients who had not received prior abiraterone or enzalutamide therapy. Inclusion criteria included histologically proven adenocarcinoma of the prostate or sclerotic bone lesions and a presenting prostate-specific antigen (PSA) > 100 ng/ml. All participants had castrate levels of testosterone (<2 nmol/L) and were receiving luteinizing hormone releasing hormone agonist therapy or had undergone surgical castration. Additionally, all participants were determined to have progressive disease, defined as a rising PSA. Patients who received an anti-androgen (flutamide or bicalutamide) as second line therapy prior to the study had to have a rising PSA above the withdrawal effect nadir when discontinuing the anti-androgen. It is also important to note that even patients who experienced radiographic progression had to meet the criterion of PSA progression, i.e. a rising PSA over 3 serum

measurements performed at least 7 days apart and within 3 months of enrolling in the study. This was a particularly important and appropriate study design criterion as the primary end point of the study was PSA response. No patients had received prior cytotoxic chemotherapy, abiraterone, or enzalutamide.

As mentioned previously, the primary endpoint of the study was PSA response, defined as a 50% decrease in PSA. Secondary endpoints included the objective response rate (by response evaluation criteria in solid tumors [RECIST] criteria) and time to PSA progression. Quality of life and pain assessments were also measured.

The study consisted of a control arm of prednisolone 5 mg twice daily, and 2 experimental arms: dexamethasone 8 mg twice daily for 3 days every 3 weeks (intermittent dexamethasone), and dexamethasone 0.5 mg daily (daily dexamethasone). Participants were initially randomized to each arm in a 1:1:1 fashion. As the study progressed it was noted that none of the first 7 participants randomized to the intermittent dexamethasone arm achieved a PSA response, thus the intermittent dexamethasone arm was closed. Consequently this study essentially consisted of two arms, the control daily prednisolone arm and the daily dexamethasone arm. Upon progression, participants in the control arm were allowed to cross-over to daily dexamethasone therapy.

Based on previous studies, the authors anticipated a 20% response rate in the control arm. The study was designed to detect a 60% response rate in the dexamethasone arms. The statistical analyses determined that 28 patients would be required in each arm to achieve 80% power to detect the anticipated difference in the treatment arms. To account for drop-out the authors planned to accrue 36 patients to each arm.

The study accrued 39 patients to the daily dexamethasone arm and 36 patients to the prednisolone arm. The 2 populations appear mostly similar; however some potential differences should be noted. Although there are no statistics to confirm a true population difference, there appears to be a slightly higher population of M0 patients in the prednisolone arm (25/36; 69%) compared to the dexamethasone arm (19/39; 49%). This difference is perhaps seen more clearly when evaluated in terms of the proportion of M1 patients in the dexamethasone arm (20/39; 51%) vs. the prednisolone arm (11/36; 31%). These data may indicate that as a population the patients in the dexamethasone arm may have had more aggressive disease than the population of patients in the control arm. Such a finding would make the study results even more clinically promising. However, the time from first-line hormone therapy to beginning study drug in the dexamethasone arm is 50 months, while it was only 39 months in the prednisolone arm. Additionally, median PSAs appear slightly higher in the control arm versus the dexamethasone arm. (This finding holds true when evaluating either of the 2 median PSAs listed in **Table 1**, though the difference between the 2 listings is not clear.) These data indicate that the population of patients in the control arm may have had slightly more aggressive disease. Thus a true difference in aggressiveness between the control and experimental populations can be neither assumed, nor excluded.

A total of 85 patients were enrolled in the study: 39 were randomized to low dose daily dexamethasone and 36 were randomized to daily prednisolone. The remaining 7 were randomized to intermittent dexamethasone, but this arm of the study was closed when the first 7 patients showed no PSA response. It was this finding that led the authors to conclude that intermittent dexamethasone or dexamethasone given at the time of chemotherapy for control of nausea in unlikely to have an effect on the tumor itself. Due to the closure of the intermittent dexamethasone arm the reported results are for the 75 patients randomized to daily prednisolone or daily dexamethasone.

In an intent-to-treat analysis 41% of patients in the dexamethasone arm achieved a PSA response, while only 22% of patients in the prednisolone arm achieved a PSA response. The authors do not indicate if these data represent a statistically significant difference. The p-value was 0.08. In the absence of additional statistical data one would assume a trend toward significance without quite reaching statistical significance. In patients evaluable for PSA response (rather than in an intent-to-treat analysis) PSA responses were achieved by 47% and 24% of patients in the dexamethasone and prednisolone arms, respectively. Again, the authors do not comment on statistical significance, however, with a p-value of 0.05 one might assume a statistically significant difference. The median time to progression was 9.7 months and 5.1 months in the dexamethasone and prednisolone arms, respectively. There is no assessment of statistical significance and the 95% confidence intervals overlap somewhat. Additionally, the hazard ratio of 1.6 has a 95% confidence interval that includes 1.0 (0.9 – 2.8), thus there again appears to be a trend toward a statistically significant difference without quite meeting that threshold. Similarly the objective response rate by RECIST criteria was 15% and 6% in the dexamethasone and prednisolone arms respectively, with a p-value of 0.6. Thus there is a possible improvement in PSA response rate, objective response rate, and time to PSA progression for dexamethasone over prednisolone. As alluded by the authors in the discussion section, in a larger study this difference may have reached statistical significance. In this study, the analysis of study endpoints may have been further improved by the inclusion of a multi-variate analysis including several demographic and clinical factors that may affect the outcomes of the study, including age, performance status, Gleason score, alkaline phosphatase level, and baseline serum PSA.

Interestingly, 23 of the 36 patients randomized to prednisolone crossed over to dexamethasone at PSA progression and 19 of those patients were evaluable for PSA response. Seven of these patients (37%) achieved a PSA response to dexamethasone, which suggests a potential role for dexamethasone even after progression on prednisone therapy. This finding should not lead one to plan a treatment regimen of prednisone followed by dexamethasone. Note that 36 patients were randomized to prednisolone and only 23 crossed over to dexamethasone. The reasons only 23 patients crossed over are not specified, but presumably some patients were unable to cross over due to severe disease

progression or even death. Additionally, only 19 of the 23 patients that did cross over were evaluable for PSA response to subsequent dexamethasone therapy. Again the reasons are not specified but presumably include severe disease progression or even death. Hence only 7 of 36 patients (19%) who initially received prednisolone were able to cross over to dexamethasone and achieve a PSA response. Unfortunately, none of the patients who progressed on dexamethasone therapy crossed over to prednisolone. This would have made an interesting comparison.

Assessments of pain scores and analgesic use were not statistically different between the 2 arms, but did trend toward significance in favor of dexamethasone.

As mentioned in the article, prior phase II studies of low-dose, daily dexamethasone have reported PSA response rates of 50–60%, with median times to PSA progression from 7 to 8 months.[4,5] Here the authors recount an impressive case of one subject who achieved a complete PSA and radiographic response to dexamethasone. The response was sustained up to the time of manuscript preparation −44 months. Though likely an outlier, the case lends credence to the use of dexamethasone monotherapy in CRPC.

The authors stated that no correlative studies were performed. This is unfortunate. As discussed by the authors, pituitary or adrenal suppression secondary to exogenous use of corticosteroids is one proposed mechanism of activity of corticosteroids in CRPC. Evaluation of pituitary and adrenal activity (eg, adrenocorticotropic hormone [ACTH] levels) between patients in the 2 arms may have shed additional light on a mechanism for potential improved efficacy of dexamethasone over prednisone. The authors also mention that glucocorticoid receptors may be involved in CRPC progression. We agree that an evaluation for a withdrawal effect after discontinuing prednisolone would improve understanding of the clinical effects reported in this study.

The univariate analysis showed PSA response to be statistically significantly associated with a lower baseline PSA ($p = 0.004$) and lower baseline alkaline phosphatase levels ($p = 0.03$). These data suggest that patients with less aggressive disease, or lower tumor burden, were more likely to respond to corticosteroid monotherapy. This is an important point that should be discussed. Patients in this study had not received prior cytotoxic chemotherapy, abiraterone, or enzalutamide. Thus the findings in this study may not necessarily translate to the clinic where most patients will have been much more heavily pretreated, likely having received some or all of the following agents: abiraterone, enzalutamide, radium-223, sipuleucel-T, docetaxel, and/or cabazitaxel.

With the numerous therapies now available for CRPC, very few patients are currently treated with glucocorticoid monotherapy. In such cases, however, the results of this study would lend one to lean toward choosing daily dexamethasone over daily prednisone/prednisolone. The lack of statistical rigor in this study, however, does not compel a whole scale change in clinical practice. A larger, definitive randomized study is warranted, but accrual would likely be too difficult given the multiple therapies currently available for metastatic CRPC. There continues to be no standard of care therapy for patients with biochemical recurrence. Given the excellent tolerability profile and existing data suggesting that patients with less aggressive disease and/or lower tumor burden may be more likely to respond, a trial of daily dexamethasone in patients with biochemical recurrence may be optimal. Importantly, as stated by the authors, an assessment of dexamethasone rather than prednisone in combination with abiraterone, docetaxel, and cabazitaxel is now necessary.

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