Impact of prednisone on toxicities and survival in metastatic castration-resistant prostate cancer: A systematic review and meta-analysis of randomized clinical trials

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Abstract

We conducted a meta-analysis of randomized trials comparing regimens that included daily oral prednisone (P) in only one arm to investigate its impact on toxicities and outcomes in metastatic castration-resistant prostate cancer (mCRPC). Five trials were identified totaling 2939 patients, of whom 1471 were randomized to an arm not containing P and 1468 received therapy containing P. There was no difference between the non-P and P groups for severe toxicities (incidence rate ratio [IRR] = 0.82, \(p = 0.712, \hat{F} = 97.9\%\)). When examining toxicities as a reason for discontinuing therapy, the non-P groups were not different from the P groups (relative risk [RR] = 1.24, \(p = 0.413, \hat{F} = 86.8\%\)). The non-P groups demonstrated no difference in OS compared to the P groups (HR = 1.09, \(p = 0.531, \hat{F} = 79.7\%\)). The meta-analysis is limited by the trial level design and small number of trials.

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Keywords: Metastatic castration-resistant prostate cancer; Prednisone; Toxicities; Survival; Randomized; Clinical trial; Meta-analysis

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1. Introduction

Daily low dose oral prednisone has been commonly employed for the therapy of men with metastatic castration-resistant prostate cancer (mCRPC). Two randomized phase III trials in the 1990s compared low dose daily oral corticosteroids (either prednisone or hydrocortisone) with the combination of corticosteroid and mitoxantrone chemotherapy [1,2]. Both trials demonstrated an improved palliative impact from the addition of mitoxantrone to corticosteroids, although corticosteroids alone did demonstrate a modest palliative benefit. Thereafter, the landmark phase III TAX327 trial comparing docetaxel-based chemotherapy with mitoxantrone-based chemotherapy administered oral prednisone (P) 10 mg daily to both arms [3]. Subsequent randomized trials attempting to combine biologic agents with docetaxel and evaluating cabazitaxel chemotherapy also administered daily P [4,5]. P was combined routinely with abiraterone acetate for a different reason, i.e. to mitigate mineralocorticoid excess [6,7].

However, the impact of P on survival, as a single agent or in combination, remains unclear. Moreover, an extended period of prednisone may induce toxicities, exacerbate comorbidities and attenuate the benefits of sipuleucel-T immunotherapy [8]. A more comprehensive study to estimate the risk of toxicities and impact on overall survival (OS) with the use of daily oral prednisone is warranted. Since a prospective trial is unlikely to be conducted to probe this issue, we performed a systematic review and meta-analysis of randomized clinical trials for mCRPC, either published or presented in major oncology conferences, which included prednisone in only one of the arms.

2. Methods

2.1. Selection of studies

An independent review of citations in the English language from PubMed/Medline from January 1966 to June 2013 was conducted. Randomized phase II and III trials comparing arms with and without P were selected. Key words included in the search were metastatic castration-resistant prostate cancer, prednisone, toxicities, survival, randomized, and clinical trial. Abstracts and virtual meeting presentations from major conferences, the most recent reports, updated manufacturer’s package inserts and clinicaltrials.gov were searched. Study quality was assessed by using the 5-point Jadad ranking system [9].

2.2. Data extraction and clinical end points

Data abstraction was conducted independently by 2 investigators (GS and CJM) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. The following events and outcomes were considered for the intention to treat population: grade ≥3 toxicities, toxicities as a reason to discontinue therapy, and OS with hazard ratios (HR).

2.3. Statistical analysis

Statistical analyses were performed by using R statistical software, version 3.0 [11,12]. Trials were considered evaluable for grade ≥3 toxicities, toxicities as a reason to discontinue therapy, and OS. The proportion of patients with those adverse outcomes and 95% confidence intervals (CIs) were derived for each arm of each study and used to calculate relative risks (RR). For the meta-analysis, both the fixed-effects model and the random-effects model were considered. The latter was calculated with the method of DerSimonian and Laird, which considers both within-study and between-study variation [13]. Statistical heterogeneity among studies included in the meta-analysis was assessed using the Cochrane’s Q statistic, and inconsistency was quantified with the I² (I-squared) statistic, which is used to describe the percentage of total variation across studies that is due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, while larger values between 0% and 100% show increasing heterogeneity [14]. The assumption of homogeneity was considered invalid for p values <0.1, and in this case, we reported summary estimates from the random-effects models. A two-tailed p value of <0.05 was considered statistically significant.

3. Results

3.1. Search results

Our search (Fig. 1) yielded a total of 5 potentially relevant randomized clinical trials in mCRPC comparing a P containing arm with an arm not containing P (Table 1) [15–19]. These trials and their intention to treat randomized population included the following: by Scher et al. comparing docetaxel (D) plus P vs. D plus DN101 (n = 953), by Higano et al. comparing DP vs. GVAX (n = 621), by Small et al. comparing DP vs. GVAX plus D (n = 394), by Fossa et al. comparing P vs. flutamide (n = 201) and by Petrylak et al. comparing mitoxantrone plus P vs. D plus estramustine phosphate (n = 770).

3.2. Trial quality

Randomized treatment allocation sequences were generated in all trials. Follow-up time was generally adequate for each trial. There were 4 trials in the low-quality group (Jadad score 2) and one trial by Scher et al. in the high quality group (Jadad score 3–5) [15].


3.3. Population characteristics

The total number of patients by intention to treat was 2939, of whom 1471 received therapy not containing P and 1468 received therapy containing P. Patients were generally required to have an ECOG performance status 0–2, adequate organ function and no brain metastasis. All 5 trials were evaluable for grade \( \geq 3 \) toxicities and toxicities as a reason to discontinue therapy. Four of the 5 trials were eligible for OS analysis, the exception being the trial by Fossa et al. due to the absence of hazard ratios.

3.4. Relative risk of toxicities and survival

When examining the incidence rate of severe toxicities (Table 1), there was no statistically significant difference between subjects in the non-P and P groups (incidence rate ratio [IRR] = 0.82, \( p = 0.712, 95\% \) CI: 0.29–2.35, \( I^2 = 97.9\% \)) (Fig. 2A). When examining toxicities as a reason for discontinuing trial therapy, subjects in non-P groups exhibited no statistically significant difference from those in the P groups (relative risk [RR] = 1.24, \( p = 0.413, 95\% \) CI: 0.74–2.10, \( I^2 = 86.8\% \)) (Fig. 3A). Subjects in the non-P groups demonstrated no statistically significant difference in OS as compared to subjects in the P groups (HR = 1.09, \( p = 0.531, 95\% \) CI: 0.84–1.41, \( I^2 = 79.7\% \)) (Fig. 4A). The Fossa et al. trial was excluded from the OS analysis since the hazard ratio was not reported, nor was enough information provided to calculate one.

3.5. Sub-analysis of toxicities and survival

A sub-analysis was conducted after excluding 2 trials: by Petrylak et al. and Higano et al., because the designs of these trials were considered to confound both the clinical endpoints evaluated in the meta-analysis: survival and toxicities [16,18]. These 2 trials included docetaxel chemotherapy in only one arm, which was the only agent known to extend survival at that time. Moreover, the presence of docetaxel in only one of the arms of these 2 trials was considered to cause a potentially significant imbalance of toxicities. The Petrylak trial also administered estramustine phosphate in combination with docetaxel, which is known to cause cardiovascular and gastrointestinal toxicities. One of these trials (Higano et al.) administered P in the D containing arm, while the other trial (Petrylak et al.) administered P in the arm not containing D. The 3 trials included in this sub-analysis (Scher et al., Small et al., Fossa et al.) had a total of 1548 patients, 774 in both the non-P arms and P arms (Table 1).

In this sub-analysis, subjects in the non-P groups exhibited a significantly higher severe toxicity incidence rate than those in the prednisone groups (IRR = 1.40, \( p = 0.007\),...
95% CI: 1.10–1.78) (Fig. 2B). These results were relatively homogenous (p > 0.2 for test of heterogeneity). When examining toxicities as a reason to discontinue therapy, the RR for non-P vs. P groups was 1.39 (p = 0.017, 95% CI: 1.06–1.82); these results were relatively homogenous (p = 0.184) (Fig. 3B). Subjects in the non-P groups had significantly decreased survival as compared to subjects in the P groups (HR = 1.35, p = 0.002, 95% CI: 1.11–1.64) and these results were relatively homogenous (p > 0.2) (Fig. 4B).

4. Discussion

The meta-analysis of randomized trials in mCRPC suggests no significant impact on severe toxicities and OS with the use of daily oral P. There was no statistically significant difference between subjects in the non-P and P groups for severe toxicities (IRR = 0.82, p = 0.712), toxicities as a reason for discontinuing trial therapy (RR = 1.24, p = 0.413) and OS (HR = 1.09, p = 0.531). A sub-analysis excluding 2 trials that contained docetaxel in only one arm demonstrated that the non-P groups exhibited significantly higher severe toxicities (IRR = 1.40, p = 0.007), higher toxicities as a reason to discontinue therapy (RR = 1.39, p = 0.017) and decreased survival as compared to subjects in the P groups (HR = 1.35, p = 0.002).

The study has the anticipated limitations of a trial level meta-analysis. Individual patient level data were unavailable to evaluate a potential differential benefit of P in those with poorer performance status or higher risk groups. Conversely, trial-level meta-analyses appear to provide results similar to individual patient level meta-analyses [20]. Moreover, individual patient level data are generally unavailable for all eligible trials for a meta-analysis, and individual level analysis of a subset of trials will lead to selection biases. The Jadad scores of 4 of the 5 trials was low, i.e. 2. However, the Jadad scoring system confers points for a double-blinded design, which may not be as relevant in trials employing survival as the primary endpoint. Publication bias could not be analyzed due to the limited number of trials. The
**Fig. 3.** Toxicity as a reason for discontinuing treatment.

### A. Overall

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fossa et al 2001</td>
<td>2.36</td>
<td>0.63; 8.88</td>
<td></td>
</tr>
<tr>
<td>Higano et al 2009</td>
<td>0.60</td>
<td>[0.46; 0.78]</td>
<td></td>
</tr>
<tr>
<td>Petrylak et al 2004</td>
<td>1.68</td>
<td>[1.11; 2.53]</td>
<td></td>
</tr>
<tr>
<td>Scher et al 2011</td>
<td>1.75</td>
<td>[1.17; 2.64]</td>
<td></td>
</tr>
<tr>
<td>Small et al 2013</td>
<td>1.10</td>
<td>[0.75; 1.60]</td>
<td></td>
</tr>
</tbody>
</table>

**Random effects model**

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.24</td>
<td>[0.74; 2.10]</td>
</tr>
</tbody>
</table>

\[I^2 = 86.8\%\]  

### B. Sub-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fossa et al 2001</td>
<td>2.36</td>
<td>0.63; 8.88</td>
<td></td>
</tr>
<tr>
<td>Scher et al 2011</td>
<td>1.75</td>
<td>[1.17; 2.64]</td>
<td></td>
</tr>
<tr>
<td>Small et al 2013</td>
<td>1.10</td>
<td>[0.75; 1.60]</td>
<td></td>
</tr>
</tbody>
</table>

**Fixed effect model**

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.39</td>
<td>[1.06; 1.82]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prednisone worse</th>
<th>Prednisone better</th>
</tr>
</thead>
</table>

randomized trials did not aim to evaluate the value of daily oral P. Hence, the other treatments given in both arms of randomized trials were not identical. The Scher and Small trials administered conventional docetaxel every 3 weeks plus P (DP) in one of the arms [15,19]. However, the experimental arms contained weekly docetaxel combined with either DN101 or GVAX. Notably, in contrast to docetaxel every 3 weeks, docetaxel administered weekly has a different toxicity profile (especially less myelosuppression) and does not appear to extend OS compared to mitoxantrone [3]. Both the Scher and Small trials reported an inferiority of OS for the experimental arms, which may be a consequence of weekly docetaxel and/or a decrement due to DN101 or GVAX. Regarding the Fossa et al. trial, the comparison of flutamide with P is not as optimal as a design comparing flutamide plus prednisone to identify effects attributable solely to P [17]. The Petrylak trial combined D with estramustine phosphate, a drug almost abandoned in mCRPC due to toxicities [16]. The P containing arm in the Petrylak trial also administered mitoxantrone, which was proven to be inferior to D plus estramustine phosphate for OS, despite toxicity advantages. Finally, the Higano trial compared DP with single agent GVAX, although most patients in the GVAX arm did subsequently receive D, which may have led to the lack of statistical difference in and confounded the OS endpoint [18]. Moreover, the experimental arm contained a highly tolerable immunotherapeutic agent, while the standard P containing arm administered a chemotherapeutic agent, docetaxel, with significant toxicities.

Differences in reporting did not permit us to compare toxicities of all grades in all 5 trials. However, we were able to evaluate the most relevant toxicities, which are grade \( \geq 3 \)
toxicities and those leading to discontinuation from trial therapy in all trials. One study reported toxicities for the intention to treat population (Scher et al.), 2 studies reported toxicities for the treated population (Petrylak, Higano) and the denominator population for toxicities was unclear for the other 2 studies (Small, Fossa). Hence, to be consistent, we used the intention to treat randomized population for all trials. The Fossa trial could not be included for OS analysis due to the lack of adequate information, i.e. hazard ratios. The sub-analysis attempted to include the 3 trials with a lower magnitude of imbalance between arms, but is also plagued by differences other than P between the arms as described above. Hence, despite the statistically higher severe toxicities and decreased survival, and a trend for higher toxicities as a reason to discontinue therapy in the non-P group of the sub-analysis, the results should be interpreted with caution due to the imbalances of agents between the arms. Given a large proportion of high grade toxicities observed in the Petrylak trial (67.5% of all events; 51.1% and 80.6% of all P and non-P group events, respectively), another sub-analysis was performed excluding this trial alone, which did not change our overall conclusions showing no significant impact on severe toxicities and OS with P (data not shown).

The utility of P has assumed greater importance recently. Questions remain regarding the efficacy of sipuleucel-T immunotherapy following or preceding P containing therapy. A randomized phase II trial reported no negative impact on the manufacture of sipuleucel-T administered concurrently or sequentially with abiraterone acetate plus P, although impact on OS is unknown [21]. A retrospective analysis of the phase III AFFIRM trial suggested that baseline P use conferred inferior survival with both placebo and enzalutamide [22]. Given that our data do not suggest a harmful impact from daily oral prednisone, the results of this AFFIRM analysis suggest that patients receiving baseline P may have been selected for more symptomatic and aggressive disease prompting the institution of P. Indeed another retrospective analysis of the COU-AA-301 phase III trial comparing P combined
<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Treatment arms</th>
<th>Total N^a</th>
<th>Jadad score</th>
<th>P arm</th>
<th>Non-P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subjects</td>
<td>Toxocities grade ≥3</td>
<td>Toxocities as a reason to discontinue therapy</td>
<td>Deaths N (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Scher [15]</td>
<td>Randomized Phase III</td>
<td>DP vs. D + DN101</td>
<td>953</td>
<td>3</td>
<td>476 (10.1)</td>
<td>33 (6.9)</td>
</tr>
<tr>
<td>Small [19]</td>
<td>Randomized Phase III</td>
<td>DP vs. D + GVAX</td>
<td>394</td>
<td>2</td>
<td>197 (35)</td>
<td>41 (20.8)</td>
</tr>
<tr>
<td>Fossa [17]</td>
<td>Randomized Phase III</td>
<td>P vs. flutamide</td>
<td>201</td>
<td>2</td>
<td>101 (7)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Petrylak [16]</td>
<td>Randomized Phase III</td>
<td>MP vs. D + EMP</td>
<td>770</td>
<td>2</td>
<td>384 (203)</td>
<td>32 (8.3)</td>
</tr>
<tr>
<td>Higano [18]</td>
<td>Randomized Phase III</td>
<td>DP vs. GVAX</td>
<td>621</td>
<td>2</td>
<td>310 (142)</td>
<td>103 (33.2)</td>
</tr>
<tr>
<td>Total</td>
<td>Randomized Phase III</td>
<td>Multiple</td>
<td>2939</td>
<td>-</td>
<td>1468 (397)</td>
<td>212 (14.4)</td>
</tr>
</tbody>
</table>

^a^ Based on the number randomized with intention to treat; Both toxicity and survival analyses were conducted on the intention to treat randomized population except Petrylak trial, which reported toxicities and survival only for eligible population and the Higano trial, which reported toxicities only for treated patients.

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Table 1
Randomized trials eligible for meta-analysis.

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Author contributions

Study concept and design: Sonpavde, Morgan.
Acquisition of data: Sonpavde, Morgan.
Analysis and interpretation of data: Charity J. Morgan, William K. Oh, Gurudatta Naik, Matthew D. Galsky, Guru Sonpavde.
Drafting of the manuscript: Sonpavde, Naik, Morgan.
Critical revision of the manuscript for important intellectual content: Charity J. Morgan, William K. Oh, Gurudatta Naik, Matthew D. Galsky, Guru Sonpavde.
Statistical analysis: Morgan.
Obtained funding: Sonpavde.
Administrative, technical, or material support: Sonpavde, Morgan.
Study supervision: Sonpavde, Morgan.

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