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Platinum Priority – Prostate Cancer

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A Randomised Phase 2 Trial of Dexamethasone Versus Prednisolone in Castration-resistant Prostate Cancer

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Abstract

Background: Prednisolone is widely used as secondary hormonal treatment for castration-resistant prostate cancer (CRPC). We hypothesised that dexamethasone, another corticosteroid, is more active.
Objective: To compare the activity of prednisolone and dexamethasone in CRPC.
Design, setting, and participants: This single-centre, randomised, phase 2 trial was performed in 82 men with chemotherapy-naïve CRPC enrolled from 2006 to 2010.
Intervention: Prednisolone 5 mg twice daily versus dexamethasone 0.5 mg once daily versus intermittent dexamethasone 8 mg twice daily on days 1–3 every 3 wk.
Outcome measurements and statistical analysis: The main end point was prostate-specific antigen (PSA) response rate. Secondary end points included time to PSA progression, radiologic response rate using Response Evaluation Criteria In Solid Tumors (RECIST), and safety.
Results and limitations: The intermittent dexamethasone arm was dropped after no response was seen in seven patients. By intention to treat, confirmed PSA response was seen in 41% versus 22% for daily dexamethasone versus prednisolone, respectively ($p = 0.08$). 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 mo on dexamethasone versus 5.1 mo on prednisolone (hazard ratio: 1.6; 95% confidence interval, 0.9–2.8). In 43 patients with measurable disease, the response rate by RECIST was 15% and 6% for dexamethasone and prednisolone, respectively ($p = 0.6$). Of 23 patients who crossed over at PSA progression on prednisolone, 7 of the 19 evaluable (37%) had a confirmed PSA response to dexamethasone. Clinically significant toxicities were rare.
Conclusions: Dexamethasone may be more active than prednisolone in CRPC. In the absence of more definitive trials, dexamethasone should be used in preference to prednisolone.
Patient summary: We compared two different steroids used for treating men with advanced prostate cancer. Our results suggest that dexamethasone may be more effective than prednisolone and that both are well tolerated.
Clinical trial registry: EUDRAC 2005-006018-16

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1. Introduction

Prednisolone is widely used as secondary hormonal treatment for patients with castration-resistant prostate cancer (CRPC) [1]. Several corticosteroids, including hydrocortisone and dexamethasone, have also achieved favourable symptomatic, biochemical, and radiologic responses [2–4]. It has been assumed that corticosteroids are active in CRPC by suppression of adrenal androgen production. Hence, one would expect any corticosteroid that suppresses adrenocorticotrophic hormone (ACTH) to be equally effective [1]. Prednisolone is also used in combination with cytotoxic chemotherapy and with abiraterone to ameliorate the toxicities of treatment in patients with metastatic CRPC [5,6].

Prednisolone has been reported in phase 2 studies to produce PSA response rates of 20–25% in patients with CRPC [3,7]. Numerous phase 3 randomised trials of systemic chemotherapy or hormonal therapy in CRPC have used prednisolone as the control intervention [5,7,8]. In these trials, the PSA response rate to prednisolone has ranged from 16% to 24%, and the median time to PSA progression has ranged from 2 mo to 6 mo [6–10]. The published activity data for prednisolone in CRPC are summarised in Table 1 [3,4,6–17].

Dexamethasone has been less well studied in the treatment of CRPC. Phase 2 studies of low-dose, daily dexamethasone have reported somewhat higher PSA response rates of 50–60%, with median time to PSA progression from 7 mo to 8 mo [4,11]. The two largest studies, including a combined total of 237 patients treated with dexamethasone as a single agent, both reported PSA response rates of around 50% [4,12]. The published activity data for low-dose, daily dexamethasone in CRPC are summarised in Table 1.

Dexamethasone has also been used intermittently at higher doses as a premedication and as an antiemetic in association with cytotoxic chemotherapy for CRPC [5]. It is unclear whether this intermittent use of dexamethasone contributes to the activity of chemotherapy for CRPC.

Current clinical data suggest that dexamethasone may be more active than prednisolone in the treatment of CRPC. We conducted a randomised phase 2 trial comparing dexamethasone and prednisolone to explore this hypothesis. We initially tested two different dose schedules for dexamethasone, given the important possibility that intermittent dexamethasone might contribute to the activity of chemotherapy for CRPC.

2. Methods

We conducted a single-centre, randomised, open-label, phase 2 trial of daily prednisolone versus daily dexamethasone versus intermittent dexamethasone in patients with CRPC. Men with either histologically proven adenocarcinoma of the prostate or sclerotic bone metastases on imaging and a presenting PSA >100 ng/ml were eligible for inclusion. All patients had a baseline PSA >5 ng/ml, castrate levels of testosterone (<2 nmol/l) on androgen deprivation therapy with luteinising hormone-releasing hormone analogues or had had bilateral orchidectomy. They had progressive disease, defined as a rising PSA using three serum PSA measurements, each obtained at least 7 d apart within 3 mo prior to the start of the trial. In accordance with the UK National Institute for Health and Clinical Excellence prostate cancer guideline, patients typically received an antiandrogen as second-line hormone therapy. Patients who were withdrawn from antiandrogen therapy also required one PSA level higher than the last prewithdrawal PSA or two consecutive increases in PSA documented after the postwithdrawal nadir ≥4 wk from treatment withdrawal if treated with flutamide and ≥6 wk if treated with bicalutamide. Patients with progression of measurable disease Response Evaluation Criteria In Solid Tumors (RECIST) or progression of bone disease were also required to fit the criteria for PSA progression. Patients were chemotherapy naïve and had not received prior abiraterone or enzalutamide. Eligibility also included life expectancy ≥3 mo, Eastern Cooperative Oncology Group (ECOG) performance status 0–3, and optimal analgesia. Exclusion criteria included external beam radiotherapy, brachytherapy, or cryotherapy within 4 wk prior to the start of the study, serious or uncontrolled coexistent nonmalignant disease, active or uncontrolled infection, a history of untreated peptic ulcer disease, inability to comply with pain scores and quality of life assessments, treatment with any investigational compound within 30 d, any previous treatment with corticosteroids for prostate cancer at any time, or any of the following treatment in the past 4 wk: antiandrogens, oestrogens, radioisotopes, or chemotherapy.

All patients had baseline investigations including medical history, physical examination, ECOG performance status, serum PSA (within 7 d of

Table 1 – Clinical studies of corticosteroids in castration-resistant prostate cancer

Study	Daily dose, mg	*n*	PSA response rate, %	Median TTPSA progression, mo
Prednisolone				
Berry et al [9]	10	60	24	4.1
Tannock et al [8]	10	81	22	-
Fossa et al [13]	20	50	26	4
de Bono et al [6]	10	398	16	6.6
Fossa et al [3]	20	101	21	3.4
Sternberg et al [7]	20	50	9	2.5
Sartor et al [14]	20	29	33	2
Ryan et al [10]	10	542	24	5.6
Dexamethasone				
Nishimura et al [11]	0.5–2	37	62	9
Storlie et al [15]	1.5–2.25	38	61	8
Morioka et al [16]	1.5	27	59	5.4
Saika et al [16]	1.5	19	28	7.3
Venkitaraman et al [4]	0.5	102	50	7.4
Shamash et al [12]	2	135	50	8.1

PSA = prostate-specific antigen; TTPSA = time to prostate-specific antigen progression.

randomisation), serum testosterone, and routine haematology and biochemistry tests including urea, creatinine, potassium, sodium, alkaline phosphatase, and blood glucose. Baseline imaging comprised chest radiograph, computed tomography (CT) of abdomen and pelvis, and bone scan. Quality of life and pain assessment were performed within 7 d of randomisation with the EuroQol EQ-5D questionnaire, the Brief Pain Inventory (BPI) pain questionnaire, and an analgesic score.

Patients were randomised in a 1:1:1 ratio among intermittent dexamethasone (8 mg twice daily for 3 d every 3 wk), daily dexamethasone (0.5 mg once daily), and prednisolone (5 mg twice daily), to be continued until biochemical progression or unacceptable toxicity. All study drugs were administered orally. Patients who developed PSA progression on prednisolone were offered crossover to daily dexamethasone. Assessments during the study were performed every 6 wk and included physical examination; toxicity assessment; ECOG performance status; serum PSA; haematology and biochemistry tests; and the EuroQol questionnaire, BPI, and analgesic score (week 6,12, and 18 only). In patients with measurable disease, CT scans of abdomen and pelvis were repeated every 12 wk until 36 wk to assess response by RECIST criteria.

The primary end point was PSA response, defined as a 50% decline in serum PSA, confirmed at least 4 wk later. Secondary end points included time to PSA progression, objective response rate using RECIST criteria, safety, and tolerability. In PSA nonresponders, progression was defined as a 25% increase over the nadir value (provided the rise was a minimum of 5 ng/ml) and confirmed by a second value at least 1 wk later. In PSA responders, progression was defined as a 50% increase over the nadir value (provided the rise was a minimum of 5 ng/ml) and confirmed by a second value at least 1 wk later. The local National Health Service research ethics committee approved the study protocol, and all patients gave written informed consent.

2.1. Statistical methods

Assuming a PSA response rate for prednisolone of 20%, the study was powered to detect a PSA response rate of 60% in each experimental arm. To detect this difference, use of the two-sided χ^2 test of equal proportions required 28 patients per group with a two-sided α of 0.025 and 80% power. We planned to recruit 36 patients per group to ensure 28 evaluable patients. Univariate analysis of predictors of PSA response was done using binary logistic regression, with a p value <0.05 considered significant. Univariate analyses of predictors of time to PSA progression were also assessed by the Cox proportional hazards model. These statistical analyses used SPSS 14 (IBM Corp, Armonk, NY, USA).

Table 2 – Patient characteristics

Characteristics	Dexamethasone	Prednisolone
No. of patients	39	36
At diagnosis		
Age, yr, median (range)	67 (55–82)	67 (51–82)
T stage, *n*		
T1/2	9	7
T3/4	18	15
Not known	12	14
M stage, *n*		
M0	19	25
M1	20	11
Gleason score, *n*		
6	6	5
7	12	12
8–10	16	18
Missing	5	1
PSA, median (range)	34 (6.2–5000)	49 (5.9–4000)
At randomisation		
Age, yr median (range)	74 (58–87)	73 (60–89)
Performance status, *n*		
0	19	20
1	12	9
2	2	2
3	0	1
Time from first-line hormone therapy, mo, median (range)	50 (7–174)	39 (7–155)
PSA nadir on first-line hormone therapy, ng/ml, median (range)	1.1 (0–101)	0.8 (0–34)
Prior radical external beam radiation therapy to prostate, *n*	11	16
Metastatic sites, no.		
Bone	27	22
Lymph node	18	14
Visceral	2	3
None	5	6
PSA, ng/ml, median (range)	22.1 (6.3–881)	48.5 (6.2–2397)
Haemoglobin, mg/dl, median (range)	13.5 (8.5–16.1)	13.5 (8.5–16.1)
Alkaline phosphatase, U/l, median (range)	77 (40–354)	84 (44–969)
Lactate dehydrogenase, U/l, median (range)	161 (99–762)	161 (125–518)
Albumin, g/l, median (range)	37 (27–41)	38 (15–43)

3. Results

A total of 82 patients consented and were enrolled in the study between April 2006 and July 2010. All patients were followed up until PSA progression, death, or a minimum of 11 mo. Thirty-nine patients were randomised to dexamethasone 0.5 mg daily, 36 patients to prednisolone 5 mg twice daily, and 7 to intermittent dexamethasone. Randomisation to the intermittent dexamethasone arm was stopped early because of lack of antitumour activity. None of the seven patients achieved a PSA response, at which point recruitment to that arm of the trial was stopped. All results below are restricted to the 75 patients randomised to the other two arms of the trial. The demographics of the study population are given in Table 2.

In the intent-to-treat analysis, PSA responses were seen in 16 of 39 patients (41%) in the dexamethasone arm compared with 8 of 36 (22%) in the prednisolone arm ($p = 0.08$). In those patients evaluable for PSA response (with at least two on-treatment PSA levels at least 1 wk apart), the response rates were 47% (16 of 34) for dexamethasone and 24% (8 of 33) for prednisolone ($p = 0.05$). Figure 1 shows a waterfall plot illustrating the maximum decline in PSA while on the study drug. On univariate analysis, PSA response was associated with lower baseline serum PSA level ($p = 0.004$) and lower baseline alkaline phosphatase level ($p = 0.03$).

Median time to PSA progression was 9.7 mo (95% confidence interval [CI], 6.3–13.1 mo) for patients randomised to dexamethasone versus 5.1 mo (95% CI, 1.8–8.3 mo) for prednisolone (hazard ratio: 1.6; 95% CI, 0.9–2.8) (Fig. 2).

Of the 36 patients randomised to prednisolone, 23 patients crossed over to dexamethasone on biochemical disease progression. Of these, 19 patients were evaluable for PSA response assessment. Seven of the 19 (37%) achieved a PSA response to dexamethasone after previous PSA progression on prednisolone.

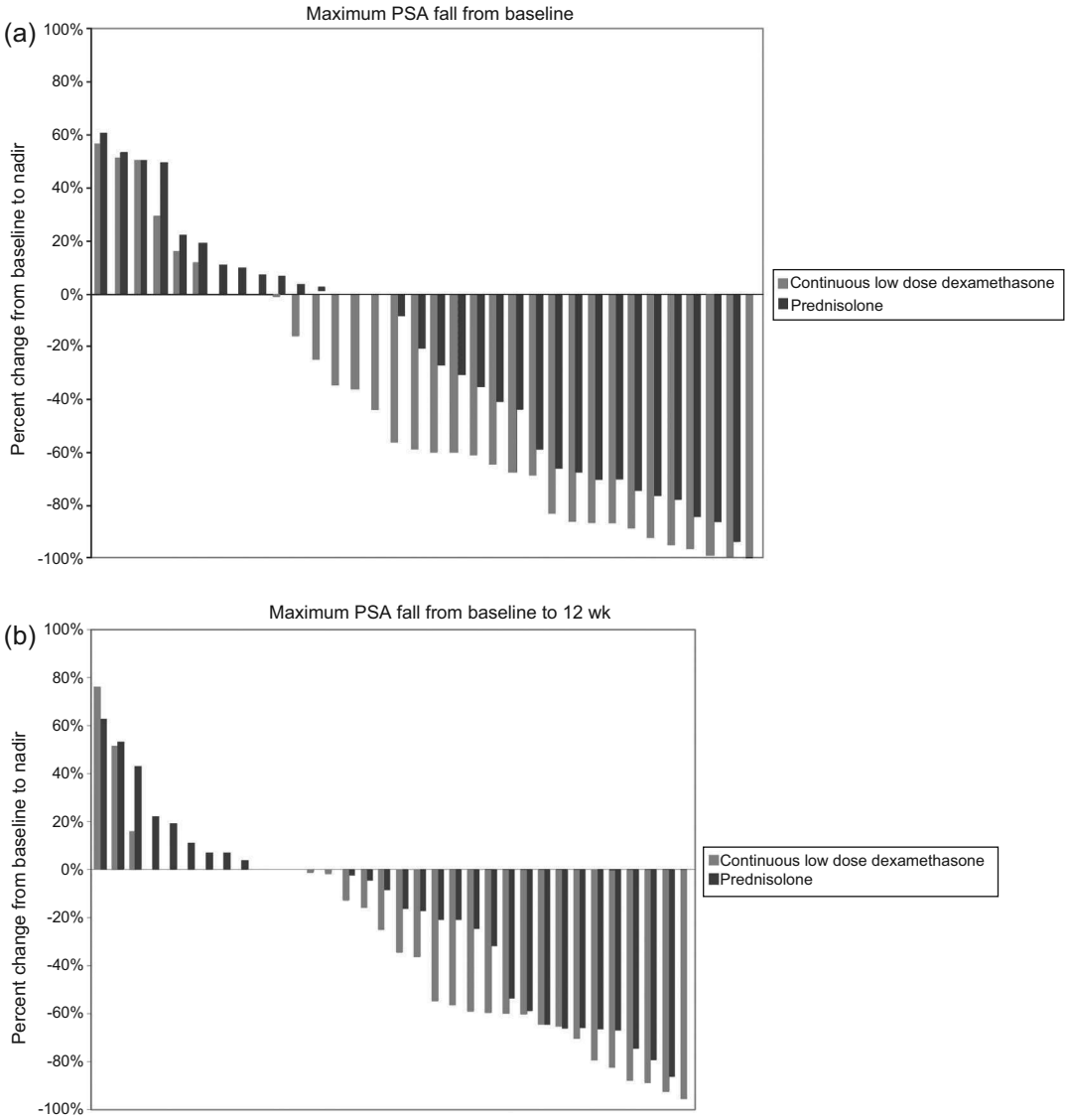

Fig. 1 – Maximum prostate-specific antigen decline by study drug (a) at any time on initial study drug treatment and (b) within the first 12 wk. PSA = prostate-specific antigen.

A total of 43 patients had measurable disease at baseline. The objective response rates by RECIST criteria were 15% (3 of 20) and 6% (1 of 18) for dexamethasone and prednisolone, respectively ($p = 0.6$). Figure 3 illustrates an objective response to dexamethasone. This patient, with a pretreatment PSA of 47 ng/ml, obtained a complete response to dexamethasone on CT scan and an undetectable PSA of <0.04 ng/ml. His serum PSA remains undetectable after treatment with dexamethasone for 44 mo.

Thirteen patients in each treatment group were on analgesia at baseline. Pain scores, analgesic use, and EQ-5D health scores improved during study treatment, with no significant difference between treatments but with a trend for greater improvement in pain for dexamethasone rather than prednisolone (Table 3). Clinically significant toxicities were uncommon (Table 4). No significant difference was seen between the two study drugs with regard to safety and tolerability. Fifty-one patients were normoglycaemic at baseline. Of these, 14 of 25 on dexamethasone had at least one glucose level >6 mmol/l versus 20 of 26 on prednisolone. Three patients on prednisolone versus none on dexamethasone had at least one random glucose level >12 mmol/l.

4. Discussion

This study is the only completed randomised comparison of different corticosteroids in CRPC. The results are consistent with the hypothesis that dexamethasone 0.5 mg daily is more active than prednisolone 10 mg daily in the treatment of CRPC. It is noteworthy that a significant proportion of patients (7 of 19, 36%) achieved a PSA response to dexamethasone after PSA progression on prednisolone.

The data are in keeping with the previously reported activity of these agents in nonrandomised clinical trials of prednisolone and dexamethasone in CRPC (Table 1). In an

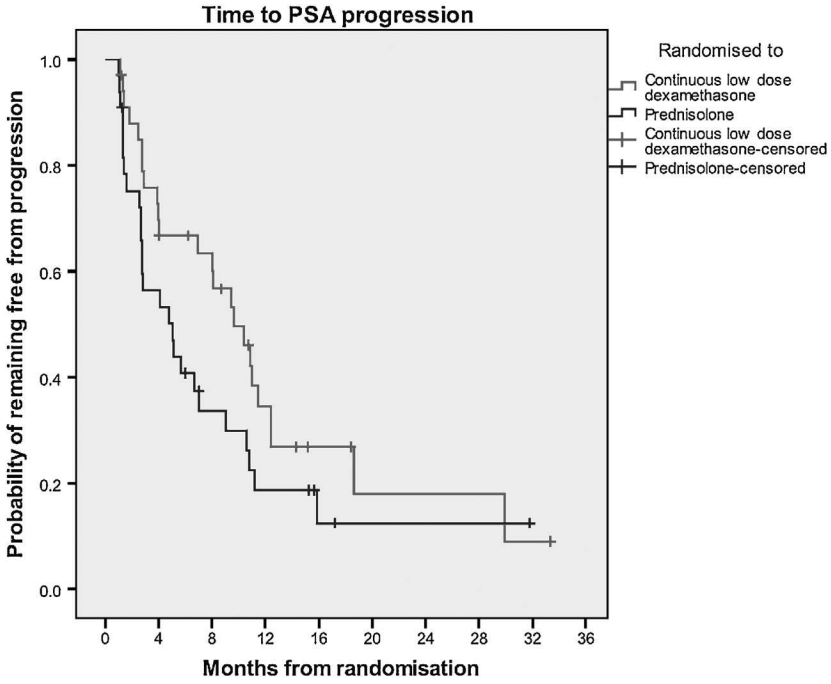

Fig. 2 – Time to prostate-specific antigen progression.
PSA = prostate-specific antigen.

early study of abiraterone treated without concomitant steroids, the addition of dexamethasone on progression was capable of inducing PSA responses [18]. Recently, the change from prednisolone to dexamethasone in patients progressing on abiraterone showed PSA declines and RECIST responses after switching steroids [19].

The current study has several limitations. Although it is the only randomised trial of corticosteroids in CRPC, it is a relatively small phase 2 trial lacking adequate statistical power to prove a real difference in activity between the two drugs. Although dexamethasone showed activity following disease progression on prednisolone, we cannot exclude the possibility that this represents a withdrawal response to stopping prednisolone. Patients did not cross over from dexamethasone to prednisolone, so we cannot comment on the activity of prednisolone after progression on dexamethasone. No correlative studies were performed, so the current study does not provide any mechanistic insights to explain how dexamethasone might be more active than prednisolone.

No responses were observed in the seven patients randomised to intermittent dexamethasone 8 mg twice daily for 3 d every 3 wk. This result is similar to data from Weitzman et al, who reported no biochemical responses in 12 patients treated with dexamethasone 20 mg three times daily for 1 d every 3 wk [20]. These observations strongly suggest that intermittent dexamethasone used either as premedication or as an antiemetic does not contribute

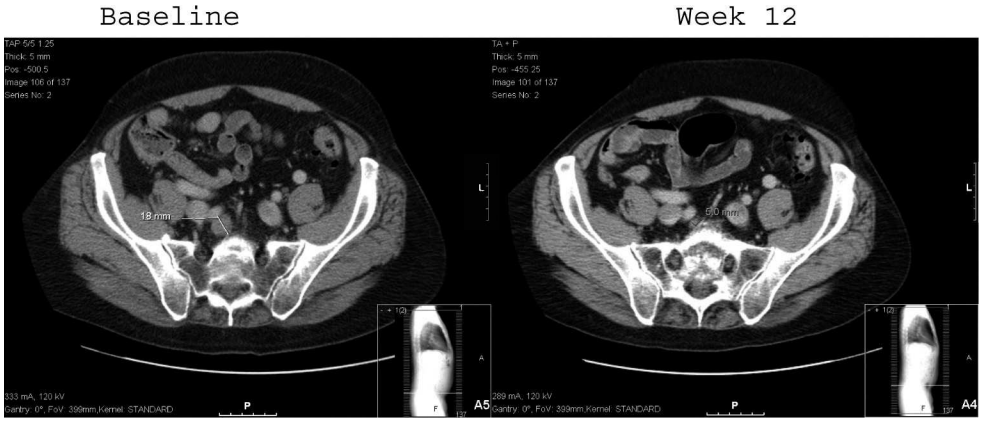

Fig. 3 – Radiologic response to dexamethasone.

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