Prednisone monotherapy in asymptomatic hormone refractory prostate cancer

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Background: *Patients with advanced prostate cancer eventually cease to respond to hormonal therapy and thus progress to hormone refractory prostate cancer (HRPC). Prednisone has been used in this setting; however, limited data is available for this monotherapy in the asymptomatic HRPC population.*

Objective: *To evaluate the PSA response rate to prednisone in asymptomatic patients with hormone refractory prostate cancer (HRPC). Secondary objectives were to determine toxicity, predictors of response, and to determine overall survival of this population.*

Methods: Patients with asymptomatic HRPC that were treated with low dose prednisone from April 1998 to 2003 were identified from the British Columbia Cancer Agency patient and pharmacy registries. Inclusion criteria were an ECOG Performance Status of ≤ 2 at the time of prednisone initiation, prior medical or surgical orchidectomy, a rising PSA, and no symptoms from prostate cancer. Demographic data, lab values, serial PSAs, and survival data were collected. Univariate analyses were performed to evaluate potential predictors of response.

Results: *Forty-nine patients met the inclusion criteria. There was a 22.4% response rate to prednisone as defined by a ≥ 50% PSA decline. An additional 16.3% of patients had a PSA decline of < 50%. Ninety percent of patients had no documented side effects. PSA responders were more likely to have bony metastases (9/11 versus 17/38, p = 0.03) and lived longer (24.7 versus 15.4 months median survival p = 0.02). The median duration of response in the PSA responders was 4.3 months (0.89-30). Of all PSA responders, 27% had a time to progression greater than 1 year and 45% did not require chemotherapy for the duration of the study.*

Conclusion: *Prednisone monotherapy is well tolerated and is associated with a clinically relevant response rate in patients with asymptomatic HRPC. Prolonged time to progression and thus avoidance of more toxic chemotherapy is possible in some patients.*

Key Words: hormone refractory prostate cancer, prednisone

Introduction

Prostate cancer is the most common malignancy in men and will account for approximately 4200 deaths in Canada this year.[1] Patients with advanced prostate cancer eventually cease to respond to medical or surgical castration and thus progress to hormone refractory prostate cancer (HRPC). The median survival of a patient with HRPC is 12-18 months.[2] Although chemotherapy for HRPC has been shown to improve survival and symptoms,[3,4] the treatment is still palliative and the associated toxicity may not be justifiable in patients who are asymptomatic. This is of greater concern when considering the frail and elderly. As such, the treatment of patients with asymptomatic HRPC has not been clearly defined.

Prednisone is used as a palliative measure that may improve symptoms such as bone pain and also exert an anti-neoplastic effect on prostate cancer.[5] The latter is achieved by inhibiting adrenal androgen production

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through negative feedback inhibition on the secretion of adrenocorticotropic hormone (ACTH).[6] Other mechanisms include the modulation of cellular growth factors and the downregulation of androgen receptor dependent transcription.[5] Thus the benefit of prednisone is not limited to the symptomatic patient because there may be anti-neoplastic effects observed in the asymptomatic population.

Several studies have evaluated prednisone therapy in HRPC patients, although most of them address the symptomatic patient. Prostate specific antigen (PSA) response rates, which are defined by a post-treatment decrease in PSA by 50% or more from baseline, have varied from 21%-34%.[7-10] Several other papers had results confounded by the concurrent use of other therapies in addition to prednisone such as high dose ketokonazole,[11] mitoxantrone,[3] and docetaxel.[3]

This study addresses the asymptomatic HRPC patient population and has been designed to evaluate their response to prednisone monotherapy. Specifically, it seeks to determine the PSA response rate, identify potential predictors of response, assess the side effect profile, and determine survival outcomes associated with prednisone therapy in patients with HRPC who have no cancer-related symptoms.

Methods and patients

This was a retrospective study. All patients with a diagnosis of prostate cancer who were treated at one of the four centers of the British Columbia Cancer Agency (BCCA) were identified. They were cross-referenced with the BCCA Provincial Pharmacy Database to find all those who were prescribed prednisone monotherapy from April 1998 to April 2003. Because the BCCA uniformly delivers and funds all cancer care throughout British Columbia, these databases provided a complete capture of the prostate cancer population treated at the BCCA.

Those patients who had asymptomatic, hormone refractory adenocarcinoma of the prostate at the time of initiation of prednisone were included in this study. Inclusion criteria were assessed first before collecting outcome data to prevent selection bias. Asymptomatic was defined as having no pain or cancer-related symptoms and an ECOG score of ≤ 2 at the time of prednisone initiation. Patients were considered hormone refractory when they had two consecutive PSA increases despite castrate levels of testosterone. All patients must have had an orchidectomy or continuing luteinizing hormone-releasing hormone (LHRH) agonist therapy. They may have had prior nonsteroidal antiandrogen (NSAA) treatment and failed either secondary to PSA progression or intolerable side effects. Patients were excluded if they had concurrent therapy with mitoxantrone, docetaxel, ketoconazole or other chemotherapy. The dose of prednisone was a total of 10 mg daily. Baseline characteristics, serial PSA levels, toxicity information, additional systemic therapy, clinical outcomes and survival information were collected in a prospectively defined database.

A PSA response was defined as a ≥ 50% reduction in the PSA when compared to the last measured value prior to starting prednisone. PSA progression was defined as a ≥ 25% increase in PSA from the baseline or a ≥ 50% increase from the nadir in patients that had a prior PSA response. Time to progression was defined as the time from starting prednisone therapy to the time of PSA progression. Overall survival was defined as the time from starting prednisone therapy to the time of death.

Fischer's Exact testing was used to determine significance of categorical demographic data. For continuous variables, the Student's T-test was performed to determine significance. Survival was estimated using the method of Kaplan and Meier and survival between responders and non-responders was compared using the log-rank test. SPSS for Windows version 12.0 was used to perform statistical analysis. All reported p values are two-sided.

Results

One hundred ninety patient charts were reviewed and 49 patients were eligible for inclusion. Median follow-up was 15.5 months (range 3.8-45 months). Five patients were still alive at the time of analysis. Patient demographic data are listed in Table 1.

There was a 22.4% response rate to prednisone with a median time to progression of 4.3 months (range 0.89-30.0 months). An additional 16.3% of patients had a PSA decline of less than 50% with a median time to progression of 2.5 months (range 0.9-10.3 months). The remaining 61.3% experienced a progressing PSA as a best response after the initiation of prednisone.

Ninety percent of the patients had no documented side effects to the prednisone. Out of the 49 patients, one had a hip fracture after 1.3 years of prednisone use, one had an upper gastrointestinal bleed after 2.5 months, two had discontinued the prednisone because of mood swings, and one stopped for unrelated reasons. There were no diabetic complications that required intervention.

PSA responders were more likely to have bony metastases (9/11 versus 17/38, p = 0.03) than non-

TABLE 1. **Demographic data and potential predictors of response in asymptomatic HRPC patients treated with prednisone grouped by whether or not there is a 50% or more decline in PSA**

Parameter	All patients n = 49 (100%)	50% PSA responders n = 11 (22.4%)	No 50% response n = 38 (77.6%)
Values at diagnosis			
Mean age	69.5	71.6	68.9
Gleason score ≤ 6[1]	8	4 (36%)	4 (11%)
Number with Gleason score > 6	26	5 (64%)	21(89%)
Metastasis when starting prednisone			
Number with bony metastases	26	9 (82%)	17 (45%) p = 0.03
Number with metastases	29	9 (82%)[2]	20 (53%)[2]
Values when starting prednisone			
Mean age	76.5	77.7	76.2
Mean time from diagnosis to prednisone (y)	7.0	6.1	7.3
Number who had previous NSAA	46	10 (91%)	36 (95%)
Number withour NSAA wash-out (if applicable)	18	1 (10%)	17 (47%)
Mean LDH (/upper limit of normal)	0.91	1.05[3]	0.86[3]
Mean ALP (/upper limit normal)	0.91	1.12	0.85
Mean hemoglobin	125	121	126
Mean PSA	279	440	233
Mean PSA doubling time (days)	213	169	216
ECOG 0	27	7 (64%)	20 (53%)
ECOG 1	16	3 (27%)	13 (34%)
ECOG 2	6	1 (9%)	5 (13%)

NSAA = non-steroidal anti-androgen; LDH = lactate dehydrogenase; ALP = alkaline phosphatase
[1]Five Gleason scores are not available; [2]p = 0.08; [3]p = 0.08

responders, Table 1. There was also a trend towards higher lactate dehydrogenase (LDH) levels and more metastatic disease in the PSA responder group although significance was not reached. There was no statistically significant difference in age, Gleason scores, lab values at the initiation of prednisone (hemoglobin, LDH, PSA, PSA doubling time), and time from diagnosis to the start of prednisone.

The median survival of this asymptomatic HRPC population given prednisone was 15.6 months. Patients that did have a PSA response to prednisone lived longer (median survival 24.7 versus 15.4 months respectively, log rank p = 0.02), Table 2 and Figure 1. Of these responding patients, 3/11 (27%) had a time to progression greater than 1 year. 5/11 (45%) responding patients did not require chemotherapy during the entire median follow-up of 24 months for these patients.

TABLE 2. **Outcome data for all patients, those who had a 50% decline in PSA with prednisone and those who did not have a 50% PSA decline**

	All patients	50% PSA responders	No 50% PSA response
Average time on prednisone (m)	11.3	16.3	9.8
Median time to progression (m)	n/a	4.3	n/a
Median overall survival (m)	15.6	24.7	15.4*

*p = 0.02 log-rank

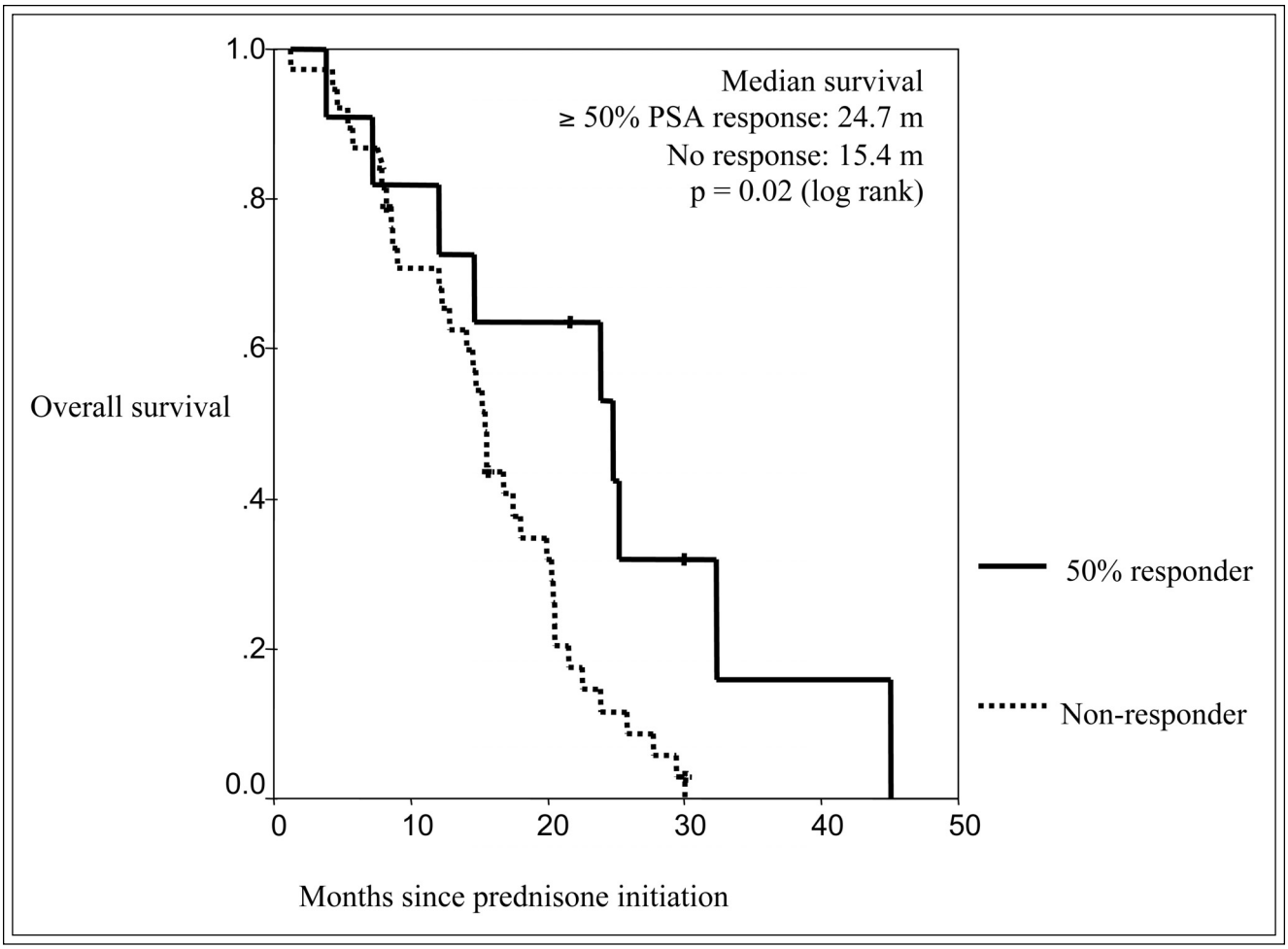

Figure 1. Kaplan-Meier curves of asymptomatic HRPC patients who did and did not have a PSA response to prednisone.

Discussion

In this retrospective study, 22% of asymptomatic HRPC patients responded to prednisone with a PSA decline of 50% or more. This is similar to data from other studies evaluating prednisone in symptomatic and asymptomatic individuals.[7-10] Of the prednisone responders, 27% had a durable time to progression of greater than 1 year.

These low doses of prednisone were well tolerated in that 90% of this asymptomatic population reported no side effects. This contrasts with the side effect profile of other agents used to treat HRPC. When comparing flutamide to prednisone in HRPC, more treatment discontinuation in the flutamide arm due to diarrhea was demonstrated.[10] Ketoconazole was associated with a 21% rate of grade 3 and 4 neuropathy, fatigue and hepatotoxicity.[12] Mitoxantrone was associated with a 48% rate of neutropenia[7] and docetaxel was associated with alopecia, vomiting, neuropathy and myelosuppression.[3]

Overall, the data suggested that patients with a higher burden of disease were more likely to respond to prednisone. This was an unexpected and counterintuitive finding. Patients with bony metastases were more likely to respond to prednisone ($p = 0.03$) and there was a trend for patients with any metastases and higher LDH values ($p = 0.08$) to be more likely to respond. Although the ranges were wide and values did not reach significance, a higher mean PSA, alkaline phosphatase and faster mean PSA doubling time was also seen in prednisone responders. Despite this, prednisone responders had improved overall survival.

Limitations of this study included the retrospective design and the reliance on the presumption of accurate and complete documentation in patient charts. This includes the difficulty in capturing all treatment related toxicities in a retrospective fashion. However our results were in agreement with other studies on the use of prednisone in the literature.[7-10]

Only one PSA measurement was used to determine PSA response in the interest of data collection feasibility. Although two measurements at least 3 to 4 weeks apart is typically used to define a PSA response, it is notable that 91% of the PSA responders had responses lasting greater than 3 months. Thus, alternative definitions of a PSA response would not meaningfully change the results.

It is possible that the PSA response was confounded by the antiandrogen withdrawal (AAW) phenomenon, which is exhibited in 11% of patients after discontinuing their antiandrogen.[12] Thirty-one patients in our study did have a standard antiandrogen wash-out period of at least 4 weeks before starting prednisone. Only one patient that did not have a suitable wash-out period exhibited a PSA response and thus it is unknown if the response was due to anti-androgen withdrawal or prednisone. Because this involved only one patient, this potential confounding factor had little impact on the data presented.

The strengths of this study included the contemporary period and context of prednisone use compared to the existing literature. We were able to capture the entire asymptomatic HRPC population of patients treated at the BCCA thereby curtailing enrollment bias and making our results more generalizable.

In summary, low dose prednisone is well tolerated and associated with a clinically relevant response in asymptomatic HRPC patients. Prednisone is a reasonable second-line hormonal treatment prior to the use of chemotherapy and is also an alternative when chemotherapy is deemed inappropriately toxic for a patient. □

References

1. Canadian Cancer Society/National Cancer Institute of Canada: Canadian Cancer Statistics 2005. Toronto: Canadian Cancer Society; 2005:16.
2. Smaletz O, Scher HI, Small EJ, Verbal DA, McMillan A, Regan K et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. *J Clin Oncol* 2002;20:3972-3982.
3. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN et al. Docetaxel plus prednisone or Mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-1512.
4. Petrylak DP, Tangen CM, Hussein MHA, Lara Jr. PN, Jones JA et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513-1520.
5. Fakih M, Johnson CS, Trump DL. Glucocorticoids and treatment of prostate cancer: a preclinical and clinical review. *Urology* 2002;60:553-561.
6. Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989;7:590-597.
7. Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. *J Urol* 2002;168:2439-2443.
8. Sartor O, Weinberger M, Moore A, Li A, Figg WD. Effect of prednisone of prostate specific antigen in patients with hormone refractory prostate cancer. *Urology* 1998;52:252-256.
9. Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;14:1756-1764.
10. Fossa SD, Slee PHT, Brausi M, Horenblas S, Hall RR, Hetherington JW et al. Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European Organization for Research and Treatment of Cancer Genitourinary Group. *J Clin Oncol* 2001;19:62-71.
11. Harris KA, Weinberg V, Bok RA, Akefuda M, Small EJ. Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer. *Urology* 2002;168:542–545.
12. Small EJ, Halabi S, Dawson NA, Stadler WM, Rini BI, Picus J et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). *J Clin Oncol* 2004;22:1025-1033.