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Treatment of Metastatic Prostatic Cancer With Low-Dose Prednisone: Evaluation of Pain and Quality of Life as Pragmatic Indices of Response

By Ian Tannock, Mary Gospodarowicz, William Meakin, Tony Panzarella, Lesley Stewart, and Walter Rider

Thirty-seven men with symptomatic bone metastases from prostate cancer that had progressed following earlier treatment with estrogens and/or orchidectomy were treated with low-dose prednisone (7.5 to 10 mg daily). The rationale for this treatment was that some patients might still have hormone-sensitive disease that was stimulated by weak androgens of adrenal origin, and that these androgens could be suppressed by prednisone through its negative feedback on secretion of adrenocorticotrophic hormone (ACTH). Response to treatment was assessed by requirement for analgesics, by the McGill-Melzack pain questionnaire, and by a series of 17 linear analog self-assessment (LASA) scales relating to pain and to various aspects of quality of life. Fourteen patients (38%) had improvement in indices used to assess pain at 1 month after starting prednisone, and seven patients (19%) maintained this improvement for 3 to 30 months (median, 4 months). Reduction in pain was associated with improvement in other dimensions of quality of life, and in the scale for overall well-being. Prednisone treatment led to a decrease in the concentration of serum testosterone in seven of nine patients where it was not initially suppressed below 2 nmol/L, and caused a decrease in serum levels of androstenedione and dehydroepiandrosterone sulfate in more than 50% of patients. Symptomatic response was associated with a decrease in serum concentration of adrenal androgens. We conclude that (1) low-dose prednisone may cause useful relief of pain in some patients with advanced prostatic cancer; (2) relief of pain was associated with suppression of adrenal androgens; and (3) measures of pain and quality of life can be used to assess possible benefits of systemic therapy in patients with metastatic prostate cancer.
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ABOUT 75% of patients with symptomatic prostate cancer will report relief of symptoms (primarily bone pain) following orchidectomy, or after initial treatment with estrogens, or luteinizing hormone-releasing hormone (LHRH) analogs. These measures reduce serum testosterone to castrate levels, thus removing the major source of androgen stimulation. The duration of response to primary androgen ablation is variable, with median values of about 1 year.[1,2] When symptoms recur, this might be due to selection of prostatic cancer cells that are hormone-independent, or to the growth of cells that are stimulated by weak androgens of adrenal origin.[3] Thus, secondary responses are sometimes observed with anti-androgens such as flutamide or cyproterone acetate,[4] following adrenalectomy,[5] or following adrenal suppression with aminoglutethimide and hydrocortisone.[6] An alternative approach is to prescribe low-dose corticosteroids[7-9] with the aim of producing negative feedback on the pituitary gland to inhibit secretion of adrenocorticotrophic hormone (ACTH). This might in turn lead to inhibition of the synthesis of the androgens androstenedione and dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), which is thought to be stimulated by ACTH. These relatively weak androgens can undergo metabolism to produce small amounts of testosterone.[3,10] Adrenal sources of androgens may account for up to 20% of activity associated with the normal testis.[3]

Assessment of response to systemic therapy of patients with prostatic cancer has been both difficult and unreliable.[11,12] Most patients do not have measurable soft tissue metastases, and serum markers such as acid and alkaline phosphatase are not consistent indices of disease activity. Many patients may report dramatic improvement in symptoms after initial hormone therapy without improvement in x-rays or bone scan. When the aim of treatment is palliation, effectiveness should be assessed optimally by reproducible indices of symptom control.

In the current study we first reviewed the

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charts of all patients with symptomatic metastatic prostate cancer who had received prednisone treatment between 1976 and 1980. Although this retrospective review revealed that some patients had major improvement in pain, there was no objective assessment of pain control (other than requirement for analgesics), and serum levels of androgens were not measured routinely. We therefore designed a prospective study with the following aims: (1) to develop methods for assessment of pain and other symptoms in patients with metastatic prostate cancer; (2) to document the probability of subjective relief of symptoms in patients receiving prednisone following progression after primary androgen ablation; and (3) to determine whether response to prednisone was correlate with a decrease in the serum levels of androgens.

METHODS

Patients

The retrospective chart review revealed that 28 patients who had undergone prior orchidectomy, or who had progressed on estrogens, were started on prednisone as treatment for symptomatic bone metastases. The charts of these patients were reviewed initially for evidence of response.

Thirty-seven patients were then entered into the prospective study. All patients had biopsy-proven prostate cancer and progressive symptomatic bone metastases despite estrogen treatment or previous orchidectomy. Patients were ineligible if they had received systemic therapy other than estrogens, or if they had life-threatening complications such as cord compression or hypercalcemia. They had to understand English (in order to complete pain and quality-of-life questionnaires). Patients with a history of diabetes or peptic ulcer disease, and those who had received corticosteroids since diagnosis of prostate cancer were excluded.

Therapy

Most patients in the retrospective series, and in the early part of the prospective study, received prednisone in a dose of 5 mg in the morning and 2.5 mg in the evening; subsequently, patients received 5 mg twice daily. Those patients who were receiving estrogen therapy continued this medication at the same dose, usually diethylstilbestrol (DES) 1 mg three times daily.

Assessment of Patients

In the retrospective series patients were classified as responding to prednisone if all of the following conditions were satisfied for a minimum period of 2 months: (1) the clinical record gave clear indication of improvement in pain; (2) there was reduced intake of analgesics; and (3) no additional therapy was required (other than continuation of estrogens).

All patients entered in the prospective study were assessed initially with a complete history and physical examination, bone scan and radiographs of painful areas. A complete blood count (CBC), and serum levels of acid and alkaline phosphatase, calcium, testosterone, androstenedione, and DHEAS were to be measured monthly. Hormone levels were measured by radioimmunoassay.

Three methods were used to assess pain prior to initiation of prednisone therapy and at monthly intervals thereafter. First, the patients were asked about their average daily intake of analgesics during the week before their clinic visit. This information was used to generate an analgesic score, representing the total daily analgesic intake. Doses of morphine (5 mg), codeine (30 mg), hydromorphone (2 mg), anileridine (25 mg), or mixed formulations containing codeine (30 mg) or oxycodone (15 mg) were assigned two points. Nonnarcotic analgesics such as aspirin (325 mg) or acetaminophen (325 mg) were assigned 1 point. The above doses may not accurately represent analgesic potency, but this does not introduce error in the present study since patients did not change medication, but merely increased or decreased the dosage.

Secondly, patients were asked to complete the McGill-Melzack pain questionnaire[13,14] under the direction of the study nurse. This questionnaire presents 20 groups of verbal descriptors relating to sensory, affective, evaluative, and miscellaneous aspects of pain (Fig 1a). Within each group the patient was asked to select one word (if any) that best described the pain that he had been experiencing during the prior week. These words were ranked in each group, and the rank values of the words selected were summed to provide the "pain rating index." A simpler assessment of pain "the present pain intensity" was selected from a 6-point verbal scale (0 = no pain, 1 = mild, 2 = discomforting, 3 = distressing, 4 = horrible, 5 = excruciating).

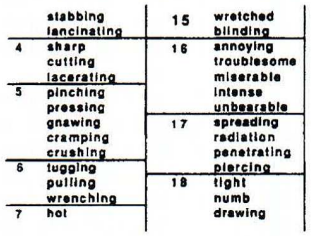
The third method for assessing pain was part of a series of 17 linear analog self-assessment (LASA) scales[15,16] (Fig 1b). For each scale the patient was presented with a 10-cm line that is anchored at its left end by the worst possible scenario (eg, extremely severe pain) and at its right end by the best possible scenario (eg, no pain at all). The patient was then asked to place a vertical mark on the line that represented his state (in relation to the end descriptors) during the preceding 24 hours. The current series of LASAs were adapted from scales that were developed and validated for use in patients with breast cancer.[16] They included scales related to general health and to symptoms of disease. We also included a global scale relating to overall well-being, which was anchored by the descriptors "extremely ill" and "I feel well." Each scale was measured in centimeters (to the nearest 0.5 cm) from its left end, so that higher scores represent less symptoms.

RESULTS

Characteristics of Patients

Characteristics of patients who were started on prednisone therapy are summarized in Table 1. Most of the patients had received extensive prior treatment, including a median of two hormonal treatments (orchidectomy and/or a variety of estrogens). Many patients had also

a. Segment of the McGill-Melzack Pain Questionnaire



b. Examples of Linear Analog Self Assessment Scales

Please place a mark on the line below to indicate your status during the past 24 hours.

8. Fatigue

extremely tired _____ not tired at all

9. Social Life, Meeting and Dealing with People Outside the Family

extremely unsatisfactory _____ completely satisfactory

Fig 1. Illustration of (a) the McGill-Melzack pain questionnaire[13] and (b) LASA scales that were used to assess pain and quality of life.

received one or more courses of radiation to bony metastases.

Tolerance of Prednisone Therapy

One patient discontinued prednisone because he claimed that it caused nausea, and a second patient experienced gastrointestinal pain. There was no observable toxicity in the remaining patients. In particular there was no gastrointestinal bleeding, and patients did not become Cushingoid with the low doses that were used.

Symptomatic Response to Prednisone

Of the 28 patients who were reviewed retrospectively, seven had improvement in pain with a reduced requirement for analgesics for a median duration of 5 months (range, 2 to 11 months).

Pretreatment values of the four indices used to assess pain in patients treated prospectively were as follows (mean ± SEM): daily analgesic score, 10.2 ± 2.2; linear analog scale, 4.3 ± 0.5; pain rating index, 21 ± 2; present pain intensity, 2.0 ±

Table 1. Characteristics of 37 Patients Treated Prospectively

Median age (range)	62 (46-76) yr
Previous therapy to primary	
Radical prostatectomy	0
Radiation to primary	12
Median no. of prior endocrine maneuvers* (range)	2 (1-4)
Median no. of irradiated metastatic sites (range)	1 (0-4)
Median interval from diagnosis (range)	27 (6-119) mo
Median interval from initial endocrine therapy* (range)	18 (4-117) mo
Subjective response to initial endocrine therapy	
Yes	25
No	4
Not assessable†	8
Initial serum concentration (range) of‡	
Acid phosphatase	2.7 (0.3-89.6) IU/L
Alkaline phosphatase	313 (76-1,000) IU/L

*Includes orchidectomy and different estrogens.

†Some patients had endocrine therapy when they were asymptomatic.

‡Normal values for serum concentration of acid and alkaline phosphatase are < 0.8 and 120 IU/L, respectively.

0.2. Thus, most of the patients were symptomatic from pain. Of 37 patients who received prednisone in the prospective study, 14 (38%) had improvement in each of the three scales that were used to assess pain, and a decreased or stable requirement for analgesics for a minimum of 1 month. Five patients became free of pain and required no analgesics. In seven patients improvement in each of the pain indices and decreased analgesic requirement persisted for 3 to 30 months (median, 4 months). Of 14 patients with initial relief of pain on prednisone, ten had responded subjectively to their initial hormonal treatment with estrogens and/or orchidectomy, one had not responded, and three could not be assessed for response.

The overall effect of prednisone on pain experienced by the entire patient population was assessed by comparing pain indices after one month of treatment with prednisone, with those recorded at the start of treatment. Statistical evaluation using the two-tailed paired *t*-test showed significant improvement in the median values of pain rating index and present pain intensity ($P = .009$ and .011, respectively) and nonsignificant trends toward improvements in analgesic score or LASA evaluation of pain ($P = .24$ and .12, respectively). The alternative statistical method of using the nonparametric sign test to compare pre- and posttreatment pain indices gave similar conclusions.

LASA scores for 13 of the 14 patients who had improvement in all indices of pain are summarized in Table 2. Initial scores were not available for one patient, but his subsequent testing showed normal or near normal scores (≥ 9) for all dimensions of quality of life. At the time of maximum improvement in pain, 46% of the scales had improved, 11% had deteriorated, and 43% were unchanged. Most of the unchanged scores reflected a normal state (before and after treatment) for some of the quality-of-life dimensions that were assessed. Large improvements were seen in the LASA scale, which reflected overall well-being by asking patients "How do you feel?" (Table 2), and all but two patients with improved pain indices had improvement in this scale. Overall, the panel of indices that were used to assess pain and quality of life provide consistent evidence for at least transient relief of symptoms in 12 of the 37 patients (32%) who received prednisone prospectively.

Biochemical Response to Prednisone

Values of alkaline and acid phosphatase were elevated initially in 31 and 22 of the 37 patients, respectively. Decreases of > 10 IU/mL in alkaline phosphatase were seen in 16 patients during prednisone therapy, but only eight of these had consistent improvement in pain. Nine patients had a decrease of > 1 IU/mL in acid phosphatase, and only four of these patients had improvement in pain. Thus there is little evidence for

Table 2. Changes in 16 LASA Scales Reflecting Different Dimensions of Quality of Life for Patients Who Had Improvement in Indices of Pain

Patient	Improved	Deteriorated	Unchanged	Change in Score for Overall Well-Being
1	11	0	5	+3.5
2	11	0	3	+4.0
3	11	1	3	+1.0
4	10	1	5	+5.5
5	9	1	5	+3.5
6	9	1	5	+2.0
7	9	2	5	+4.0
8	6	4	5	+2.0
9	5	7	4	−1.5
10	4	0	10	+6.5
11	3	0	12	+1.0
12	3	3	9	−1.0
13	0	1	13	+4.0
Total	91	21	84	

*For dimensions, see Table 4. Some dimensions (eg, employment) were not relevant to some individuals and were not scored. Initial LASA scores were not available for one patient who had complete resolution of pain at 1 month.

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