Health-Related Quality of Life in Men With Metastatic Prostate Cancer Treated With Prednisone Alone or Mitoxantrone and Prednisone

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Purpose: **A combination of mitoxantrone plus prednisone is preferable to prednisone alone for reduction of pain in men with metastatic, hormone-resistant, prostate cancer. The purpose of this study was to assess the effects of these treatments on health-related quality of life (HQL).**

Patients and Methods: **Men with metastatic prostate cancer (n = 161) were randomized to receive either daily prednisone alone or mitoxantrone (every 3 weeks) plus prednisone. Those who received prednisone alone could have mitoxantrone added after 6 weeks if there was no improvement in pain. HQL was assessed before treatment initiation and then every 3 weeks using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC QLQ-C30) and the Quality of Life Module–Prostate 14 (QOLM-P14), a trial-specific module developed for this study. An intent-to-treat analysis was used to determine the mean duration of HQL improvement and differences in improvement duration between groups of patients.**

Results: **At 6 weeks, both groups showed improvement in several HQL domains, and only physical functioning and pain were better in the mitoxantrone-plus-prednisone group than in the prednisone-alone group. After 6 weeks, patients taking prednisone showed no improvement in HQL scores, whereas those taking mitoxantrone plus prednisone showed significant improvements in global quality of life ($P = .009$), four functioning domains, and nine symptoms ($.001 < P < .01$), and the improvement (> 10 units on a scale of 0 to100) lasted longer than in the prednisone-alone group ($.004 < P < .05$). The addition of mitoxantrone to prednisone after failure of prednisone alone was associated with improvements in pain, pain impact, pain relief, insomnia, and global quality of life ($.001 < P < .003$).**

Conclusion: **Treatment with mitoxantrone plus prednisone was associated with greater and longer-lasting improvement in several HQL domains and symptoms than treatment with prednisone alone.**

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IN A RANDOMIZED STUDY conducted in multiple Canadian institutions, therapy with a combination of mitoxantrone and prednisone was shown to be preferable to treatment with prednisone alone for the palliation of pain in men with hormone-resistant, metastatic prostate cancer.[1] A palliative response was defined as a decrease in pain on a self-assessment pain scale without an increase in analgesic medication, which was maintained for two consecutive evaluations at least 3 weeks apart. A secondary end point was a decrease in analgesic use without an increase in pain, and other health-related quality-of-life (HQL) parameters were evaluated by patient self-assessment using the Prostate Cancer–Specific Quality-of-Life Instrument (PROSQOLI),[1,2] the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire C30 (QLQ-C30),[3,4] and a trial-specific module of questions (Quality of Life Module–Prostate 14 [QOLM-P14]) designed for this study.

In the previous report, the emphasis was placed on the primary and secondary end points, and the quality-of-life results were described only briefly.[1] As shown by changes in the PROSQOLI Linear Analog Self-Assessment scores and the QLQ-C30 scores, treatment with mitoxantrone plus prednisone was favored over prednisone alone for pain relief, physical activity or function, constipation, and mood. Patients in both treatment arms who met the criteria for a palliative response had improvement in most HQL domains, but details of the nature of the improvements and their duration were not described.

Here we present a detailed analysis of HQL as measured by the QLQ-C30 and the trial-specific module. Analysis of quality-of-life data was performed to obtain information about the following questions: (1) Was there a difference in HQL between the patients treated with mitoxantrone plus prednisone compared with prednisone alone at 6 weeks of therapy, ie, before patients treated with prednisone were

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eligible for the addition of mitoxantrone? (2) Was HQL improved in patients who continued on treatment with mitoxantrone and prednisone, and if so, which domains continued to show improvement and for how long? (3) Was HQL maintained in patients who continued treatment with prednisone alone? (4) Was there an improvement in HQL in patients in whom mitoxantrone was added after the failure of prednisone alone?

PATIENTS AND METHODS

Patient Characteristics and Treatment

The characteristics of the patient population were described previously.[1] Briefly, 161 men with metastatic adenocarcinoma of the prostate, who had symptoms that included pain and disease progression despite standard hormonal therapy, were randomized to receive mitoxantrone (12 mg/m^2 given intravenously every 3 weeks) and prednisone (5 mg orally twice daily) (80 patients) or prednisone alone (81 patients). In addition to other eligibility criteria, the patients had to be willing and able to complete pain and HQL questionnaires.

The treatment of the patients in the study was described in detail previously.[1] Briefly, patients continued their primary androgen ablation therapy, and most patients had discontinued additional antiandrogen treatment. Midway through the study, flutamide withdrawal response was recognized; thereafter, patients were monitored for at least 4 weeks after stopping flutamide before being entered onto the study. Two responding patients who entered earlier in the study discontinued flutamide less than 4 weeks before entry.

Patients were examined in the clinic every 3 weeks. Analgesic medication was adjusted to give optimum pain control before entry and throughout the study. All analgesic medications were recorded by the patients in a diary, which was used to compute an analgesic score representing mean daily analgesic use during the previous week. Use of dexamethasone and other corticosteroids was not allowed for antiemetic medication. Dosages of mitoxantrone were adjusted according to granulocyte and platelet nadirs. Patients with no improvement in pain or those with progressive symptoms after treatment with prednisone alone at 6 weeks were eligible to have mitoxantrone added to the prednisone. The study was not blinded because it was deemed inappropriate to give control patients sham injections of colored fluid.

Primary End Point

The primary indicator of palliation was pain relief as measured by a two-point reduction in the six-point Present Pain Intensity Scale of the McGill Pain Questionnaire[3] or complete relief of pain if 1+ initially, without an increase in analgesic score maintained on two consecutive visits at least 3 weeks apart. A decrease of 50% in the analgesic score for at least two consecutive evaluations 3 weeks apart was used as a secondary criterion in a response. The results of the primary and secondary criteria for the primary end point were reported elsewhere.[1] This report deals entirely with the results of the HQL measurements using the QLQ-C30 and QOLM-P14.

Quality-of-Life Questionnaires

Patients completed two questionnaires, the EORTC QLQ-C30 and a module of 14 items designed for men with hormone-resistant, metastatic prostate cancer (QOLM-P14), without assistance in the clinic at each 3-week visit. The QLQ-C30 is a 30-item, previously validated questionnaire with five domains pertaining to functioning, ie, physical, role, emotional, cognitive, and social, as well as a separate global quality-of-life domain.[4,5] In addition, there are three symptom domains consisting of fatigue, pain, and nausea/vomiting and six single items about appetite, insomnia, diarrhea, constipation, dyspnea, and financial impact.

The QLQ-C30 was supplemented by the QOLM-P14, which consisted of 14 items related to symptoms from metastatic prostate cancer and side effects of analgesics and chemotherapy that are not covered by the QLQ-C30 (Appendix). These items were derived by interviewing 10 men with advanced prostate cancer who were attending a support group to obtain information about their concerns. A semistructured format was used to ask what was of importance to their HQL and to list their issues. Twenty issues, many related to each other but not covered by the QLQ-C30, were identified. From these issues, 12 items were written and reviewed by oncologists who care for patients with prostate cancer. An item on difficulty passing urine and one on the extent to which having to pass urine at night disturbed sleep were added to the questionnaire halfway through the study, after it was discovered that they had been inadvertently left out at the beginning. As a first step, before an analysis of the HQL data was performed, an evaluation of the psychometric properties of the original 12 QOLM-P14 items was conducted on the data set of responses obtained in the trial. Questionnaire structure and scaling errors were examined by a principal components factor analysis, including orthogonal varimax rotation,[6] and by a multitreat scaling analysis.[7] Three scales (impact of pain on mobility, pain relief, and drowsiness) and two single items (hair loss and change in taste) were identified. Internal consistency estimates as assessed by Cronbach's alpha coefficient were 0.88 for impact on pain mobility, 0.72 for pain relief, and 0.68 for drowsiness. The two items added during the study (nocturia and effect of nocturia on sleep) were not included in the factor analysis and were analyzed as single items.

The QLQ-C30 was scored according to previously described methodology.[4,8] The raw scores were transformed to provide a range between 0 and 100; higher scores for the functioning and global quality-of-life scales indicated better functioning, whereas higher scores for the symptom scales and items indicated more of each symptom. After factor and scaling analysis of the QOLM-P14, the scoring of the resulting scales and single items was performed in a similar fashion to that of the QLQ-C30.

Patients also completed a nine-item linear analog self-assessment instrument, the PROSQOLI.[1,2] A comparison of this assessment method with the QLQ-C30 was reported elsewhere.[2]

HQL Analyses

An SAS program (SAS Institute, Cary, NC) was used to perform the statistical analyses. Baseline QLQ-C30 and QOLM-P14 scores were determined for each patient before therapy was started. New baseline scores were calculated for patients who began treatment with prednisone but had mitoxantrone added at 6 weeks or later by using the last score before the addition of mitoxantrone. Subsequently, a description of the scores for patients on each treatment arm was obtained at the completion of two cycles (6 weeks) of chemotherapy or 6 weeks of prednisone. Comparisons were then made between the scores at a given cycle and the baseline scores for the same patients within each treatment group. Both parametric and nonparametric statistics were used for these comparisons, but because these two methods did not give rise to any significant discrepancies, only the results of the parametric methods (analysis of variance) are reported. In the aforementioned comparisons,

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formal corrections were not applied for multiple significance testing. Instead, we used a *P* value of .01 to identify probable differences between groups of data, although *P* values less than .05 are reported.

The proportions of patients in each treatment group who had a change of at least 10 units in either domain or item scores (possible range, 0 to 100) on at least two successive measurements were calculated.[9] This degree of change is probably meaningful to patients because it is easily perceptible to them and may therefore be clinically important. Another study using different methodology[10] also supports the contention that a change of greater than 10 units in QLQ-C30 domain scores is clinically important, and studies in other illnesses indicate that changes of this magnitude are clinically meaningful.[11-13]

The mean duration of change (± 2 SE) for each group was determined by an intent-to-treat analysis. To calculate the duration of change, each patient who experienced a change of greater than 10 units lasting for at least two treatment cycles (6 weeks) was counted only once, and data from patients who experienced a change at any cycle followed by no further data (off treatment or death) were excluded. The mean duration of change was calculated by summing the duration of change for all patients and dividing by the number of patients randomized to the group. Statistical comparisons for the mean duration of change between the intent-to-treat groups were not attempted because the data were not normally distributed. We did not use nonparametric methods for these analyses because it seemed unreasonable to assign median values of zero to a group in which the majority of patients did not have an improvement of greater than 10 in a given HQL score.

In addition to assessing the mean duration of change in HQL scores for the treatment groups on an intent-to-treat basis, we also assessed the duration of a change of greater than 10 only in patients who experienced it. This was accomplished by plotting the proportions of patients who were still experiencing this degree of change as a function of time, rounded to 3-week intervals (the timing of the assessments), and comparing the resulting curves by the log-rank test in a manner analogous to that used for comparison of survival curves.

Participating investigators were unaware of individual HQL scores while the study was being conducted, and the analysis of HQL data was performed only after the study was closed to accrual.

Table 1. Patient Characteristics

Characteristic	Prednisone (n = 81) No.	%	Mitoxantrone and Prednisone (n = 80) No.	%
Age, years				
Median	67		69	
Interquartile range	64-74		63-75	
Site of metastases				
Bone	77	95	78	98
Lymph nodes	15	19	18	22
Visceral	3	4	3	4
Other	8	10	7	9
Time from diagnoses, years				
Median	2.9		3.0	
Interquartile range	1.5-4.6		1.6-5.1	
ECOG performance status				
0	3	4	5	6
1	47	59	45	57
2	22	28	21	26
3	8	10	8	10
Unknown	1	1	1	1
Present pain intensity				
0	1	1	1	1
1	23	28	30	38
2	37	46	30	38
3	15	19	15	19
4	5	6	4	5
Analgesic score*				
Median	14		18	
Interquartile range	6-24		10-30	

NOTE. The protocol required patients to be symptomatic with pain at entry onto the study, but case report forms indicated 2 patients without pain, and 8 patients were judged to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0.

*Calculated from a pain diary or the average daily intake over the prior week using a score of 2 for standard doses of narcotics (eg, morphine 10 mg) and a score of 1 for standard doses of nonnarcotics (eg, acetaminophen 325 mg).

RESULTS

Characteristics at Baseline

The characteristics of the 161 men who participated in the trial that are of importance for the quality-of-life assessment are listed in Table 1. Most characteristics were well balanced, except that there was a trend for patients who had been randomized to the mitoxantrone-plus-prednisone arm to have a higher analgesic score than those treated with prednisone alone. Details of the baseline QLQ-C30 and QOLM-P14 scores indicated no apparent differences between the groups in any of the functioning scales, global quality-of-life scale, and symptoms (Table 2).

Intergroup Comparison of HQL After 6 Weeks of Therapy

Patients who were randomized to receive only prednisone were required to take it for at least 6 weeks before becoming eligible for the addition of mitoxantrone because of symptomatic progression or lack of improvement in pain. However, three patients in the prednisone group had mitoxantrone added before the completion of 6 weeks of treatment with prednisone. These three patients were included in the prednisone group for the 6-week and intent-to-treat analyses.

Of the 81 patients randomized to the prednisone arm, 62 remained in this arm after 6 weeks, compared with 71 of the 80 patients randomized to the combined treatment arm. The difference in attrition rates (23% *v* 11%) creates bias when attempting a between-groups analysis in the conventional manner, because the patients who were doing well were more likely to remain on study. Therefore, a statistical analysis of these differences was not attempted, but a description of the HQL results in patients who completed 6 weeks of prednisone or of mitoxantrone plus prednisone (two cycles) is provided, using two different methods.

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Table 2. Baseline (Pretreatment) QLQ-C30 and QOLM-P14 Scores

Scales and Items	Prednisone		Mitoxantrone and Prednisone	
	No.	Mean ± SD*	No.	Mean ± SD*
QLQ-C30				
Functioning†				
Physical	81	53.3 ± 26.8	80	50.0 ± 25.8§
Role	78	44.2 ± 33.2	78	45.5 ± 38.8
Emotional	81	70.7 ± 19.7	80	68.1 ± 19.9
Cognitive	80	78.1 ± 20.3	79	73.4 ± 23.0
Social	78	60.0 ± 28.5	80	58.1 ± 28.7
Global QL	81	45.4 ± 21.3	79	44.2 ± 21.2
Symptoms‡				
Fatigue	81	50.7 ± 23.6	80	50.1 ± 20.1
N/V	80	17.5 ± 24.4	80	18.3 ± 22.0
Pain	80	51.0 ± 24.8	79	50.4 ± 27.3
Dyspnea	80	28.3 ± 27.1	79	26.6 ± 25.3
Insomnia	81	30.5 ± 30.4	80	26.3 ± 29.4
Anorexia	79	34.6 ± 32.7	79	38.4 ± 36.6
Constipation	81	39.1 ± 34.1	80	46.3 ± 32.0
Diarrhea	81	7.8 ± 16.9	79	9.3 ± 22.0
Financial Impact	81	18.1 ± 27.4	80	13.8 ± 25.8
QOLM-P14‡				
Pain impact	80	40.1 ± 24.0	80	43.0 ± 23.7
Pain relief	75	26.2 ± 21.3	77	29.0 ± 22.4
Drowsiness	79	38.4 ± 20.1	80	40.3 ± 19.3
Hair loss	74	0.9 ± 7.7	79	3.0 ± 12.2
Change in taste	79	16.0 ± 26.1	79	23.2 ± 33.1
Dysuria	39	14.5 ± 23.9	45	11.1 ± 20.1
Nocturia/sleep	38	48.2 ± 34.4	45	37.8 ± 26.2

*On a scale of 0 to 100.

†For the functioning and global quality-of-life scales, higher scores indicate better functioning.

‡For the symptom scales and items, higher scores indicate more of the symptom.

§*P* values for comparisons between groups for each scale and item were > .05.

In the first method, the mean scores were calculated for each treatment group. The mean values for each score in both groups were similar, although patients who received mitoxantrone plus prednisone apparently experienced more distress from hair loss (mean scores ± SD, 9.0 ± 19.6 *v* 1.1 ± 6.0) and a change in taste (mean scores ± SD, 24.6 ± 28.4 *v* 12.5 ± 22.6), whereas those who received only prednisone had more difficulty with insomnia (mean scores ± SD, 28.0 ± 28.4 *v* 19.2 ± 25.6). In the second method, we examined the differences in the change in scores from baseline to the 6-week time point in both groups. The baseline scores for each patient were subtracted from the scores at 6 weeks and the means of differences were calculated for each group. Thus, each patient served as his own control. The advantage of this method over the previous one is that it accounts for variations in individual baseline values between patients (whether or not the group baseline values are statistically significantly different between groups). Compared with the prednisone-only group, the mitoxantrone-plus-prednisone group apparently showed improvement in physical functioning (mean change from baseline ± 2 SE, +8.4 ± 2.3 *v* −1.1 ± 3.2) but greater hair loss (+6.8 ± 2.5 *v* –0.6 ± 1.4) and greater nocturia leading to sleep disturbance (+4.6 ± 4.6 *v* −9.0 ± 3.5).

Changes in HQL as Compared With Baseline

Further analyses were conducted in patients who continued prednisone treatment after 6 weeks, those who continued on mitoxantrone plus prednisone, and those who had crossed over from prednisone to mitoxantrone plus prednisone at any time during the study. These analyses required calculation of a new baseline value for each patient who had crossed over, ie, the score obtained on the last HQL assessment just before the cross-over regardless of when it occurred. A total of 48 patients crossed over to the mitoxantrone-plus-prednisone group, but one of these patients had missing baseline HQL scores and another had baseline scores but did not provide any further HQL scores after baseline. The new baseline scores for the cross-over group were not significantly different from the original baseline scores for either the original prednisone or the mitoxantrone-plus-prednisone groups, except for a higher pain score. This would be expected in the cross-over group because failure of improvement in pain was the primary reason for adding mitoxantrone.

In the following analysis, the differences between the baseline scores and scores after each even-numbered (second, fourth, and sixth) cycle of treatment were calculated for each of the three treatment groups, ie, patients who started and continued on prednisone alone or on mitoxantrone plus prednisone and those who had mitoxantrone added (the cross-over group). The comparison between baseline and each treatment cycle assesses the degree and duration of improvements in HQL at specific time points in patients who continued on treatment. Thus, it is not a comparison between groups by intent to treat but, rather, a comparison of scores within the groups of patients remaining on study and their own pretreatment scores.

Of the patients who remained on treatment after 6 weeks of therapy (two cycles), the group treated with prednisone alone (n = 62) showed improvements in social functioning, global quality of life, nausea and vomiting, anorexia (.003 < *P* < .007), and the impact that pain had on their mobility (*P* = .01) compared with baseline scores (Fig 1). The group treated with mitoxantrone plus prednisone (n = 71) showed an improvement in physical functioning, social functioning, global quality of life, pain, anorexia, constipation, the impact of pain on mobility, the degree of pain relief, and

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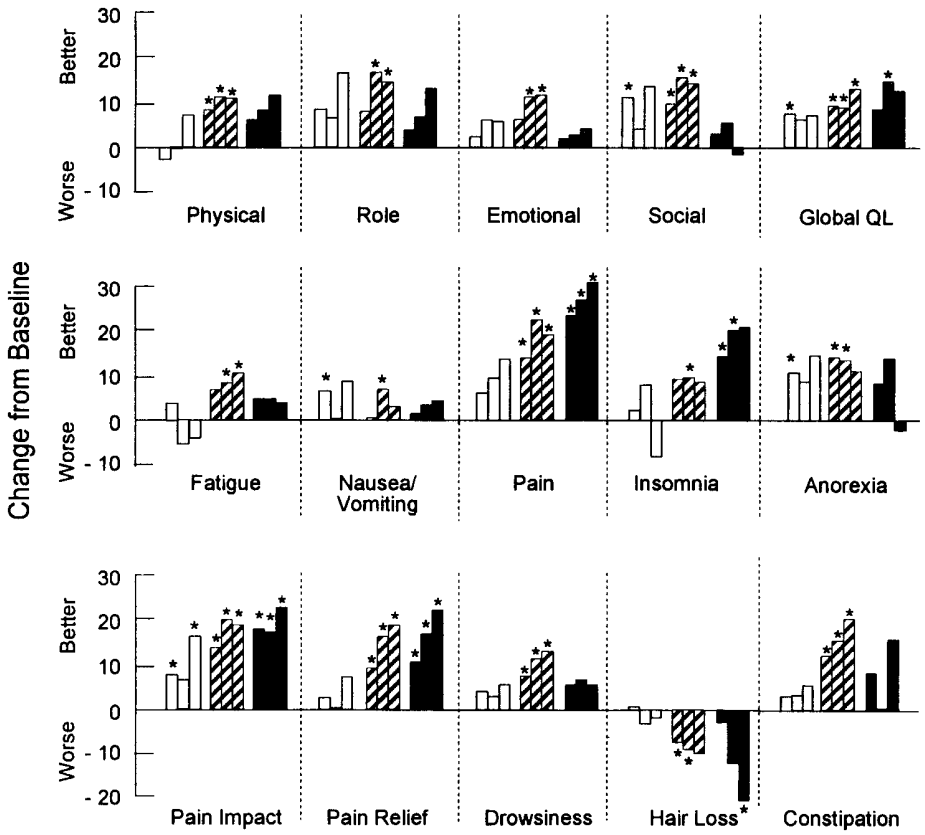

Fig 1. Mean change in QLQ-C30 scores for patients taking prednisone alone (□), prednisone plus mitoxantrone (▨), and mitoxantrone added to prednisone (■). Changes were calculated from baseline to treatment cycles 2 (first bar in each triplet of bars), 4 (second bar), and 6 (third bar). Improvements in scores are above the 0 horizontal line. Asterisks indicate *P* values ≥ .01 for the change from baseline.

drowsiness ($.0001 < P < .009$). This group experienced an increase in hair loss as the only statistically significant deleterious effect ($P = .009$; Fig 1). Six weeks after the addition of mitoxantrone, the cross-over group (n = 35) experienced an improvement in pain, insomnia, and the impact of pain on mobility ($.0001 < P < .01$; Fig 1). Only comparisons with differences reaching a significance level of $P = .01$ are emphasized, although several other comparisons of differences, particularly in the mitoxantrone-plus-prednisone and cross-over groups, showed *P* values of $.01 < P < .05$.

After 12 weeks of therapy (four completed cycles), there was no statistically significant improvement, as compared with baseline, in any of the HQL scores in the group still being treated with prednisone (n = 42), although there was an insignificant decrease in pain ($P = .05$; Fig 1). However, the group that continued to be treated with mitoxantrone plus prednisone from randomization (n = 54) showed continuing improvement over baseline in four functioning scores ($.0001 < P < .004$), global quality of life ($P = .009$), and nine symptoms ($.0001 < P < .01$). The only deterioration was in hair loss ($P = .001$). The cross-over group (n = 25) had an improvement in global quality of life ($P = .003$) as well as in pain relief ($P = .0001$).

After 18 weeks of therapy (six completed cycles), the small number of patients still receiving prednisone (n = 19) had improvement only in the impact of pain on mobility ($P = .004$) as compared with baseline (Fig 1). Those receiving mitoxantrone plus prednisone (n = 43) continued to have an improvement in 11 of the 14 function and symptom scales that had improved after cycle 4. The small number of cross-over patients (n = 17) still remaining on study after 18 weeks of mitoxantrone therapy continued to have improvement in pain, impact of pain on mobility, and pain relief ($.001 < P < .003$) but had significantly greater hair loss ($P = .01$).

Duration of Change in HQL Scores

In addition to indicating which groups of patients experienced the greatest magnitude of improvement in HQL, the data in Fig 1 show that the change in some domains lasted longer in the mitoxantrone-plus-prednisone group than in

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