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ARTICLES

Quality of Life in Advanced Prostate Cancer: Results of a Randomized Therapeutic Trial

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Background: For patients with metastatic prostate cancer, treatment is primarily palliative, relying mainly on the suppression of systemic androgen hormone levels. To help document the achievement of palliation and to characterize positive and negative effects of treatment, we evaluated quality-of-life (QOL) parameters in patients with metastatic prostate cancer who were randomly assigned to two methods of androgen deprivation. **Methods:** Patients ($n = 739$) with stage M₁ (bone or soft tissue metastasis) prostate cancer were enrolled in a QOL protocol that was a companion to Southwest Oncology Group INT-0105, a randomized double-blind trial comparing treatment with bilateral orchiectomy (surgical castration) plus either flutamide or placebo. Patients completed a comprehensive battery of QOL questionnaires at random assignment to treatment and at 1, 3, and 6 months later. Data were collected on three treatment-specific symptoms (diarrhea, gas pain, and body image), on physical functioning, and on emotional functioning. All P values are two-sided. **Results:** Questionnaire return rates for this study never dropped below 80%; only 2% of the patients did not submit baseline QOL assessments. Cross-sectional analyses (corrected for multiple testing) identified statistically significant differences that favored orchiectomy plus placebo for two of the five primary QOL parameters as follows: patients receiving flutamide reported more diarrhea at 3 months ($P = .001$) and worse emotional functioning at 3 and 6 months (both $P < .003$). Longitudinal analyses replicated these findings. Other analyzed QOL parameters favored the group receiving placebo but were not statistically significant after adjustment for multiple testing. **Conclusions:** We found a consistent pattern of better QOL outcomes at each follow-up assessment during the first 6 months of treatment for orchiectomized patients with metastatic prostate cancer who received placebo versus flutamide. Improvement over time was evident in both treatment groups but more so for patients receiving placebo. [J Natl Cancer Inst 1998;90:1537-44]

Cancer of the prostate is the most common cancer in men (excluding nonmelanomatous skin cancer) with approximately 210 000 new cases expected to be diagnosed during 1997 (1). For patients with metastatic prostate cancer, treatment is primarily palliative (2). Endocrine manipulations remain the standard approach, and these manipulations rely primarily on suppression

of androgens, which can be accomplished by medical or surgical castration alone or combined with other treatments (3).

In a previous Southwest Oncology Group (SWOG) trial (INT-0036), patients with stage M₁ disease were randomly assigned to receive treatment with medical castration (leuprolide acetate) and either flutamide or placebo. Patients receiving treatment with medical castration and flutamide (i.e., in the flutamide arm) had superior survival and progression-free survival (4). Quality-of-life (QOL) outcomes were not measured in that study.

This article presents QOL results obtained in the successor trial INT-0105, in which surgical castration (orchiectomy) was substituted for leuprolide acetate in a double-blind design (5).

Most treatments are accompanied by treatment-related side effects. Patient-reported measurements can help document the extent to which such toxic effects affect the patient's QOL. For flutamide, previous research has documented diarrhea, gas pain, and gynecomastia (affecting body image) as prevalent side effects (4). In other studies (3,6-9), sexual dysfunction, pain, fatigue, urinary tract symptoms, and psychosocial adjustment problems have been reported by patients with metastatic disease. In one study (8), patients with metastatic prostate cancer reported more severe pain than did those with other metastatic cancers.

This study added reliable and valid measures of patient-reported QOL to the survival assessment of the therapeutic trial. QOL data help document achievement of palliation and, regard-

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less of survival results, differentially characterize both positive and negative effects of treatment (2,10). QOL data supplement information provided by traditional clinical outcomes and provide information for treatment decisions made by physicians and patients.

METHODS

Sample and Eligibility Criteria

INT-0105 is a randomized, double-blind, placebo-controlled phase III trial in which patients with stage M₁ carcinoma of the prostate were enrolled in a protocol comparing either treatment with bilateral orchiectomy and flutamide or treatment with bilateral orchiectomy and placebo. Patients enrolled in trial INT-0105 were eligible to register for trial S9039, a QOL companion study. Eligibility requirements for INT-0105 were as follows: histologically proven adenocarcinoma of the prostate; stage M₁ disease (bone or soft tissue metastasis); SWOG performance status of 0–3 (where 0 is full activity); adequate renal function and white blood cell count; no prior or concomitant use of hormonal therapy, chemotherapy, or biologic response modifiers; and no other cancers within the past 5 years (nonmelanomatous skin cancer excepted) (5).

Design and Objectives

The overall objective of this QOL study was to examine the effect on patient-reported QOL of treatment involving bilateral orchiectomy and flutamide compared with treatment involving bilateral orchiectomy and placebo during the initial 6 months of treatment on this protocol. The QOL protocol specified the following five primary QOL parameters (i.e., outcomes) that were assessed three times during the study: three treatment-specific symptoms (diarrhea, gas pain, and body image), emotional functioning, and physical functioning. The protocol-specified *a priori* hypotheses associated with these primary outcomes and the three assessment periods are described below. The trial was also designed to measure general symptom status, pain, fatigue, and urinary functioning.

The SWOG QOL Questionnaire was administered at treatment randomization (baseline) and at 1, 3, and 6 months later. Median progression-free survival for patients in the castration-only arm (i.e., group) was estimated to be 13.9 months based on data obtained in a previous trial, INT-0036 (4). To minimize missing data as a result of deterioration of health status and death, we set the final QOL assessment at 6 months when approximately 75% of the patients in the control arm should be progression free and 95% should be alive. Patients were likely to have required clinic visits for treatment and follow-up throughout the 6-month period, which would facilitate completion of QOL questionnaires.

QOL Assessment Methods

The SWOG QOL Questionnaire was designed after reviewing existing QOL questionnaires for appropriate item content, adequate psychometric properties, and feasibility for use in a cooperative group (10). Patient questionnaires were self-administered. The patient-reported measure of QOL is comprehensive, addressing several dimensions of patient functioning (10–15). The SWOG QOL Questionnaire is a battery of standardized measures, including the Symptom Distress Scale (SDS) (16–20). The total score of the SDS provides a measure of general symptom status; higher scores reflect a worse symptom status.

Four areas of general functioning are also included in the SWOG QOL Questionnaire: the Short Form-36 (SF-36) Physical Functioning Scale (21–25); the SF-36 Mental Health Index (MHI) (21–25); the SF-20 Role Functioning Scale (21,22); and the SF-36 Social Functioning Scale (23–25). The total scores for each of the four functioning areas provide four QOL outcomes, with Physical Functioning and the MHI (emotional functioning) scores designated as two of five primary QOL outcomes. Higher scores for these scales reflect better functioning. The SWOG QOL studies were initiated during the transition between the SF-20 and the SF-36 in consultation with the developers of these questionnaires; this included a decision to change the time frame of the SF-20 and SF-36 scales from 1 month to 1 week (there is now a 1-week time frame version of the SF-36; Ware JE Jr: personal communication). Internal consistency reliability coefficients for the physical (.94), emotional (.84), role (.92), and social functioning (.72) scales and the SDS (.84) have been documented for the advanced prostate cancer patients described in this article (26).

In addition, 15 treatment-specific symptom items were developed with input from SWOG nurses and physicians and received pilot testing. These items are

reported as single items (i.e., are not scored as a module) and in this format are analogous to the report of physician-rated toxic effects. Three of the 15 symptom items were designated primary outcomes (diarrhea, gas pain, and concerns with body image). Quality-control procedures have been described elsewhere (10,26,27).

Statistical Methods

Cross-sectional analyses. The five primary outcomes (diarrhea, gas pain, body image, physical functioning, and emotional functioning) were compared for the two treatment arms at 1, 3, and 6 months after treatment randomization. The three symptoms were frequently observed side effects associated with antiandrogen treatment. Physical functioning and emotional functioning provide two summary measures of overall patient functioning, extending the scope of treatment evaluation beyond the realm of symptoms and side effects. Because five primary outcomes were tested at each of three time points, a Bonferroni factor of 15 was used to adjust the probability level for rejecting the null hypothesis at the traditional 5% (two-sided) α level to .003 (28). Power was estimated to be adequate for primary comparisons.

For physical and emotional functioning total scores, Wilcoxon rank sum tests were used to examine the differences at three time points. For the three symptom variables, dichotomies of these response choices for each symptom were created for each of the three time points. On the basis of a patient's selection of one of five response levels for each symptom, we classified patients into those reporting severe problems with the symptom versus those not reporting severe problems. Definitions for each primary symptom dichotomy are provided below. The estimated probability of a severe symptom problem is accompanied by a 95% confidence interval (CI) reflecting the precision of the probability estimate for that arm. Chi-squared tests were used to test the difference in incidence of severe problems in the two arms of the study. These tests were conducted with a significance level of .003. 1) Diarrhea: not frequent (seldom more than two normal stools per day to occasional diarrhea [two or three loose stools per day, no more than once per week]) versus diarrhea that is fairly frequent (two or three loose stools per day several times a week), frequent (two or three loose or watery stools daily), or very frequent (more than three watery stools daily); note: patients with a colostomy were excluded; 2) gas pain: not frequent (seldom if ever or occasional [no more than once a week] gas pain) versus frequent (several times a week, once or several times a day); and 3) concern with body image or appearance: not frequent (no change in appearance or occasional concern) versus frequent (often, most of the time, or constant concern that appearance is worsening).

Results for other single-item dichotomous symptom measures are presented as descriptive only without *P* values because they were not planned comparisons. As for the primary symptoms, the estimated probability of patients selecting response levels 1 or 2 (not considered a severe problem) versus 3, 4, or 5 (considered a severe problem) is presented along with the 95% CI for precision of that estimate for that arm of the study. Probability estimates and 95% CIs are also presented for a dichotomized version of the SDS total score. A patient was considered to have elevated symptom status if his SDS score was greater than 25. SDS totals above 24–26 points have been found by the developer of the questionnaire to reflect clinically meaningful symptom problems (McCorkle R: personal communication).

Longitudinal analyses. We conducted longitudinal analyses to confirm the results of the planned cross-sectional analyses. Longitudinal analyses are preferred because they address two factors that affect the power of statistical tests—even with randomization, treatment arms can differ on the psychosocial outcome measures at baseline; individual patient differences can, in some instances, overwhelm between-group or treatment-arm differences. Generalized estimating equations (29) were used to analyze the repeated QOL measures and symptom scores. Generalized estimating equations can account for the correlation among repeated measurements on a single subject and allow the usual modeling of the mean in terms of covariates, such as time, treatment, severity of disease (minimal versus extensive), and performance status (0–2 versus 3) (30). All of the models were estimated by using an unspecified covariance structure with robust sandwich variance estimators. For the two continuous measures, emotional functioning and physical functioning, the square root transformation was used to satisfy more closely the assumption of normality. For the three binary symptom variables indicating frequency of poor body image, diarrhea, and gas pain, we assumed a binomial distribution with a logistic link function. Because five models were fit, the probability level for statistically significant covariate effects was adjusted to .01. All *P* values are two-sided.

Missing data. Data presented in this article are based on statistical methods that depend on adequate questionnaire submission rates and missing data patterns that are not dependent on patient health status. The questionnaire submission rate at each time point was computed as a percentage of questionnaires due at that time point. Missing data within QOL scales with total scores were handled as follows. If a patient failed to answer 20% or fewer items for a scale, his score for that scale was calculated as the mean of the remaining items. If the patient left blank more than 20% of the items, his total score for that particular assessment time was considered missing. In general, conclusions about the QOL of patients with advanced-stage prostate cancer do not appear to be biased by the tendency of patients with the poorest QOL to drop out (analyses not shown). Average values for each QOL outcome at each time were compared for patients who completed all assessments, patients who failed to complete all assessments as a result of death or deteriorating health, and patients who failed to complete all assessments for other reasons. Of the five primary outcomes, only the physical functioning measure suggested the presence of nonignorable missing data. Therefore, we considered it appropriate to conduct the confirmatory longitudinal analyses described above.

RESULTS

Therapeutic Trial Results

The therapeutic trial INT-0105, activated in December 1989 and closed in September 1994, accrued 1387 patients; 700 were randomly assigned to receive orchiectomy plus flutamide and 687 were randomly assigned to receive orchiectomy plus placebo. No statistically significant survival differences were detected when the arms of this trial were compared (5).

QOL Accrual

All patients who registered after October 1, 1990, for INT-0105 registered also for the QOL companion study; the QOL study also closed September 15, 1994. The QOL study sample of 739 patients exceeded the planned sample of 500 patients. Two patients were excluded from analysis because they were ineligible for the therapeutic study.

Patient Characteristics

Patient characteristics are summarized in Table 1. Pretreatment demographic and clinical data (e.g., overall eligibility status, treatment status, prior surgery, prior radiation therapy, prior systemic therapy, and clinical stage) were compared for the therapeutic ($n = 1387$) and QOL ($n = 737$) groups. Although there were statistically significantly more patients in the flutamide arm with extensive disease ($P = .011$), this difference did not affect conclusions regarding treatment effects on QOL described below. The distributions of baseline demographic and clinical variables of the 737 patients in the QOL sample were similar to the distributions in the therapeutic sample (data not shown).

QOL Questionnaire Submission Rates

Table 2 shows questionnaire submission rates for the four assessment times. Questionnaire submission rates for this trial never dropped below 80%. Only 15 (2%) of the 737 patients did not submit baseline QOL assessments.

Cross-Sectional Analyses

Protocol-designated primary end points are presented in Table 3. A significance level of $P < .003$ was required for determining statistical significance of differences between treatment arms for primary end points.

Table 1. Patient characteristics in the quality-of-life study*

Characteristic	Flutamide arm	Placebo arm
Age, y		
Median	70	70
Minimum–maximum range	45–92	43–90
Race, No. (%)†		
White (non-Hispanic)	271 (75)	265 (73)
African-American	89 (25)	91 (25)
Other	3 (0)	5 (2)
Performance status (%)‡		
0–2	356 (96)	350 (95)
3	14 (4)	17 (5)
Severity of disease (%)§		
Minimal	67 (18)	95 (26)
Extensive	303 (82)	272 (74)

* $n = 737$ eligible patients.

†Totals do not include unknown race.

‡Performance status: 0 = full activity; 1 = restricted in strenuous activity but ambulatory and able to do light work; 2 = ambulatory and capable of self-care but unable to work; 3 = capable of only limited self-care, in bed, or confined to a chair more than 50% of waking hours.

§Severity of disease: minimal, evidence of pelvic and axial skeletal involvement on bone scan and/or nodal metastasis; extensive, appendicular (with or without axial) skeletal involvement and/or visceral (lung, liver) metastasis.

Table 2. Quality-of-life (QOL) questionnaire submission rates*

Assessment time	No. of patients alive	Questionnaires submitted, %†
Baseline	737	98
1 mo	733	88
3 mo	723	86
6 mo	705	81

*Various completion patterns for follow-up QOL questionnaires were observed for the three treatment-specific symptoms and two QOL total scores. The number of patients per pattern varied with the specific QOL outcome measure.

†Percentage of questionnaires submitted at each assessment point took into account that the patient was alive and on study long enough to complete the scheduled questionnaire.

Table 3, A, presents the probability estimates for severe symptom problems (primary symptoms) in each treatment arm; 95% CIs portray the precision of each estimate. It is important to note that the majority of patients did not report severe problems (i.e., they reported “none” to “occasional problems” for these symptoms).

Frequent diarrhea was reported statistically significantly more often by patients receiving flutamide (estimated probability = .09) versus placebo (estimated probability = .03) at 3 months after treatment randomization ($P = .001$). Differences at other follow-up times were in the hypothesized direction but were not statistically significant after Bonferroni adjustment.

No statistically significant differences in reports of gas pain were detected for patients receiving flutamide versus placebo at any of the follow-up assessments, although differences were in the hypothesized direction (e.g., more gas pain with flutamide; $P = .005$ at 1 month).

The potential side effect of gynecomastia associated with flutamide was measured by concern with body image; however, most patients did not report body image problems. Concern with body image did not statistically significantly differ by treatment arm, although the percentage of patients reporting this problem

Table 3. Primary quality-of-life outcomes

A. Symptoms*							
Assessment time	Flutamide			Placebo			P
	Prob. est.	95% CI	n	Prob. est.	95% CI	n	
Frequent diarrhea							
Baseline	.04	.02–.06	359	.03	.01–.05	346	.33
1 mo	.04	.02–.06	324	.03	.01–.05	313	.43
3 mo	.09	.06–.12	314	.03	.01–.05	302	.001
6 mo	.07	.04–.10	287	.04	.02–.06	272	.08
Frequent gas pain							
Baseline	.19	.15–.23	357	.22	.18–.26	352	.35
1 mo	.22	.17–.27	321	.14	.10–.18	317	.005
3 mo	.22	.17–.27	316	.16	.12–.20	301	.03
6 mo	.22	.17–.27	286	.19	.14–.24	270	.41
Frequent concern: body image							
Baseline	.08	.05–.11	362	.10	.07–.13	356	.47
1 mo	.04	.02–.06	326	.03	.01–.05	317	.42
3 mo	.03	.01–.05	317	.02	.004–.04	302	.49
6 mo	.07	.04–.10	291	.03	.01–.05	276	.03
B. Mental Health Index total score†							
Assessment time	Flutamide			Placebo			P
	Mdn	25 th –75 th percentile	n	Mdn	25 th –75 th percentile	n	
Baseline	76	56–88	363	76	56–88	352	.71
1 mo	76	60–88	325	80	68–92	315	.004
3 mo	80	60–92	313	84	72–92	301	.001
6 mo	76	60–88	291	84	68–92	274	.002
C. Physical Functioning total score†							
Assessment time	Flutamide			Placebo			P
	Mdn	25 th –75 th percentile	n	Mdn	25 th –75 th percentile	n	
Baseline	64	30–85	364	65	30–85	355	.50
1 mo	60	35–85	325	65	40–88	318	.27
3 mo	60	39–85	317	70	40–90	304	.05
6 mo	65	40–85	287	75	40–90	275	.05

*Estimates of the probability of severe problems with the indicated symptom; the 95% confidence intervals (CIs) are for the probability estimates (Prob. est.); n = number of patients; P value for the χ^2 test of treatment arm differences in incidence of severe problems.

†Median (Mdn) scores; n = number of patients. Higher scores reflect better functioning.

was higher in the flutamide arm at all three follow-up assessments. A smaller percentage of patients in both arms reported frequent concern with appearance at follow-up assessments. This pattern held at all three follow-up assessments for patients in the placebo arm, but in the flutamide arm, the percentage at 6 months was similar to that at baseline.

The MHI measured the emotional-functioning component of QOL in this trial (Table 3, B). Patients receiving flutamide reported statistically significantly lower (worse) MHI scores than did patients receiving placebo at two of three follow-up assessments (both $P < .003$); the difference at 1 month was in the hypothesized direction ($P = .004$). Patients who received flutamide did not report statistically significantly worse physical functioning (lower scores) than patients receiving placebo, but the difference was in the expected direction at 1, 3, and 6 months (Table 3, C).

Table 4 presents the probability estimates for six additional symptom outcomes designated as secondary. In general, symptoms improved for patients in both arms with more improvement in the placebo arm. Patients receiving placebo reported less frequent and intense pain. Not only did patients receiving flutamide report more problems with fatigue than did patients

receiving placebo, but also patients receiving placebo showed improvement in fatigue over time. Reports of incontinence (placebo slightly lower incidence) and frequency of urination (flutamide slightly lower incidence) appeared relatively similar. There were more patients receiving flutamide who reported total SDS scores greater than 25, a cutoff score reflecting clinically important symptom status; higher SDS scores reflect more symptom problems. These differences were not compared statistically because the SDS total score was not a primary end point.

In summary, of cross-sectional analyses, for the 15 primary QOL outcomes, there were three statistically significant differences favoring the placebo arm at less than the adjusted P value of .003 and six additional differences that favored the placebo arm of the trial with P values between .003 and .05 (see Table 3). The remaining primary comparisons favored the placebo arm but differences had P values greater than .05. The consistency of the effect favoring patients who received placebo—that is, they had lower symptom scores and higher scores for emotional and physical functioning—is particularly interesting given its emergence above and beyond any effects associated with having an orchiectomy. Of the 18 dichotomized

Table 4. Additional treatment-specific symptoms

Assessment time	<i>A. Symptom*</i>					
	Flutamide			Placebo		
	Prob. est.	95% CI	n	Prob. est.	95% CI	n
Frequent pain						
Baseline	.48	.43–.53	362	.45	.40–.50	355
1 mo	.35	.30–.40	327	.29	.24–.34	316
3 mo	.34	.29–.39	315	.24	.19–.29	302
6 mo	.33	.28–.38	292	.29	.24–.34	273
Intense pain						
Baseline	.35	.30–.40	361	.34	.29–.39	355
1 mo	.20	.16–.24	326	.15	.11–.19	315
3 mo	.23	.18–.28	315	.19	.15–.23	302
6 mo	.22	.17–.27	291	.19	.14–.24	273
Fatigue						
Baseline	.32	.27–.37	360	.34	.29–.39	355
1 mo	.31	.26–.36	326	.23	.18–.28	317
3 mo	.29	.24–.34	315	.26	.21–.31	302
6 mo	.32	.27–.37	290	.25	.20–.30	275
Incontinence						
Baseline	.13	.09–.17	341	.10	.07–.13	338
1 mo	.09	.06–.12	316	.07	.04–.10	310
3 mo	.09	.06–.12	311	.07	.04–.10	299
6 mo	.09	.06–.12	283	.05	.02–.08	273
Frequent urination						
Baseline	.24	.19–.29	340	.24	.19–.29	336
1 mo	.20	.16–.24	314	.22	.17–.27	305
3 mo	.20	.16–.24	308	.25	.20–.30	298
6 mo	.21	.16–.26	284	.24	.19–.29	271
SDS ≥ 25						
Baseline	.23	.19–.27	359	.21	.17–.25	354
1 mo	.15	.11–.19	325	.05	.03–.07	317
3 mo	.12	.08–.16	315	.09	.06–.12	300
6 mo	.17	.13–.21	290	.12	.08–.16	274
<i>B. Median SDS total score†</i>						
Assessment time	Flutamide			Placebo		
	Mdn	25 th –75 th percentile	n	Mdn	25 th –75 th percentile	n
Baseline	19	14–24	359	18	15–23	354
1 mo	17	13–21	325	16	13–19	317
3 mo	17	13–21	315	15	13–19	300
6 mo	17	13–21	290	16	13–19	274

*Estimates of the probability (Prob. est.) of severe problems with the indicated symptom; the 95% confidence intervals (CIs) are for the probability estimates; n = number of patients; SDS is the Symptom Distress Scale.

†Median (Mdn) scores; n = number of patients. Higher scores reflect worse functioning.

untested symptom outcomes, only two favored the flutamide arm. These untested comparisons are consistent with the primary outcome findings of worse QOL for orchiectomized patients receiving flutamide than for orchiectomized patients receiving placebo.

Longitudinal Analyses

Longitudinal models for all time points confirmed the results of the cross-sectional analyses. For all outcomes, except gas pain, there was a statistically significant time effect, indicating improvement with time, though not necessarily linear improvement; this is also shown in Tables 3 and 4. The presence or absence of a treatment difference by arm was confirmed in every case. Statistically significant treatment effects were found for the emotional functioning scale and the dichotomous diarrhea item, both in favor of the placebo arm. Longitudinal analyses adjusted

for severity of disease; in no case were conclusions regarding the five primary outcomes affected.

DISCUSSION

This QOL study was designed as a companion to the SWOG-coordinated intergroup trial INT-0105. The therapeutic trial failed to demonstrate the initially hypothesized benefits of conventional end points (survival and progression-free survival) ascribed to combined treatment with bilateral orchiectomy and flutamide over orchiectomy alone (5). In addition to evaluating efficacy in an advanced-stage disease trial, researchers are interested in the extent to which a new treatment improves disease-related symptoms while limiting discomfort associated with treatment. Although most patients in this trial reported improved QOL over time, the patients receiving flutamide tended to show less improvement for most QOL dimensions, particularly in the area of emotional functioning. With respect to treatment-related

morbidity, patients treated with orchiectomy and flutamide showed statistically significantly more severe problems with diarrhea at 3 months than did those treated with orchiectomy and placebo. That is, the QOL data strongly suggest that the QOL benefit conferred by orchiectomy over the 6-month treatment period was reduced when flutamide was added.

Our study documented that QOL assessment in this population is feasible and that compliance with the scheduled assessments was very good. In this study, we did not experience the severe missing data patterns observed in other advanced-stage disease trials (31,32), further increasing confidence in the QOL results. Questionnaire submission rates for this trial, which never dropped below 80%, generated data at follow-up time points that, in general, were unbiased with respect to health status. Therefore, the dataset could accommodate a broader range of analysis approaches, allowing an examination of longitudinal effects on QOL. These QOL submission rates were achieved in the cooperative group/multisite context where quality control procedures are difficult to implement. In a previous SWOG trial in advanced colorectal cancer, missing data were nonignorable and longitudinal analyses could not be done (32).

The submission rates also support the relevance of the questionnaire for patients being treated for advanced prostate cancer. At the time this study was designed in 1989, there were few validated prostate cancer-specific symptom modules. Items developed by Fowler et al. (33) were designed to measure QOL and symptom status for benign prostatic hyperplasia. As indicated above, the SWOG prostate items were generated by clinicians and nurses based on expected symptoms associated with hormonal treatment and the natural course of advanced-staged prostate cancer. Since 1990, the measurement properties of several prostate-specific modules have been published (34–36), providing researchers with good options for measuring the effect of prostate cancer treatment on symptom status. Results from this trial indicated the ability of the prostate cancer treatment items to detect treatment-arm differences, if not always at the conservative *P* values adopted for this trial.

A possible limitation of this study is the 6-month follow-up period in which we assessed effects of treatment on QOL. To see whether the observed treatment effects persist over time, we need to assess QOL for 1 and 2 years after treatment randomization. Several ongoing SWOG studies include QOL outcomes in the context of intermittent versus continuous total androgen blockade; these studies have a longer follow-up period and will add to the information obtained in this study. The submission rates obtained for QOL questionnaires indicate that selection of 6 months as a stopping point for QOL assessments minimized missing data and allowed for a more comprehensive analysis approach.

Overall, this trial indicated that the addition of flutamide to bilateral orchiectomy had a number of patient-reported negative effects on QOL: symptom problems (particularly diarrhea) and less positive reports for the more global measures of QOL (i.e., emotional functioning) occurred during the initial 6 months of protocol treatment. Only a decreased frequency of urination favored the flutamide arm. The diarrhea findings confirm the incidence of diarrhea associated with flutamide (physician toxicity ratings) reported in our previous study (4) and in the current therapeutic trial (5), but overall the incidence of severe diarrhea

was low. In the QOL study, there was more extensive disease in patients receiving flutamide than in patients receiving placebo. Extent of disease, however, was controlled for in the longitudinal analyses and did not affect conclusions drawn regarding treatment-arm differences for the QOL outcomes.

QOL outcomes showed improvement over the 6-month period in both treatment arms in the trial; this may reflect the effect of bilateral orchiectomy. For example, pain, fatigue, and the SDS total score showed improvement (less so for incontinence and frequency of urination) as did emotional and physical functioning. Patients receiving flutamide versus placebo tended to show less improvement for most QOL dimensions, suggesting that this agent detracts from the palliative effect achieved by bilateral orchiectomy alone.

We originally hypothesized that patients receiving treatment with orchiectomy and flutamide would have worse emotional and physical functioning than those receiving treatment with orchiectomy and placebo because we expected that side effects associated with flutamide (e.g., diarrhea) would extend to the more global QOL domains, compromising emotional and physical functioning. More patients receiving flutamide discontinued treatment compared with patients receiving placebo (33 versus 10 patients), suggesting that some patients had problems tolerating flutamide. Reduction of symptoms that may be disease related (e.g., pain) can also extend to improvements in broader QOL domains. Heim and Oei (8) reported that patients with prostate cancer who had more pain reported more emotional dysfunction. We examined the association between a three-level emotional functioning variable and dichotomized diarrhea, pain intensity, and pain frequency items. The association, although not uniformly statistically significant by arm and time for diarrhea, was statistically significant for the two pain variables and, in general, held for both treatment arms. It is, therefore, possible that flutamide could affect emotional functioning indirectly by causing side effects or by not palliating disease-related symptoms as well as another treatment. However, we did not have a large enough sample to test all the pertinent interaction terms, nor did we have sufficient data to address causality.

Effects of hormone manipulation on emotional functioning and well-being similar to those observed in our study have been previously reported. Hirshkowitz et al. (37), in their review of the limited data supporting associations between affect/mood states and testosterone levels, reported that correlational studies have yielded mixed conclusions, but some experimental studies support decreased symptoms of depression with testosterone treatment. They suggested that androgen blockade treatment in men offered a good opportunity to study these effects. Such studies are under way. Three studies with small sample sizes have reported neuropsychiatric morbidity when an antiandrogen agent was used (38–40). In one phase II trial of antiandrogen monotherapy (flutamide), severe depression was reported for four of 17 patients, resulting in cessation of therapy for two of the four patients (38). Two pilot studies involving intermittent androgen suppression (39,40) reported compromised well-being while on therapy and improvements in well-being with cessation of treatment. For example, in a pilot study reported by Higano et al. (39), treatment with leuprolide plus flutamide resulted in emotional lability, depression, and negative changes in well-being that were reported by both the patient and his spouse; eight

of nine patients reported improvement in these areas on discontinuation of androgen deprivation. [As mentioned above, SWOG currently is conducting a trial of intermittent androgen suppression using a luteinizing-hormone-releasing hormone agonist and an antiandrogen (41). QOL is being measured in the trial for a 2-year period, and the QOL results should be informative.]

It is possible that flutamide's effect on emotional functioning is not mediated by symptom status but is more direct. Of interest, then, is a mechanism by which a direct link could occur. Flutamide is a nonsteroidal antiandrogen that blocks androgen effects. Because testosterone can also be produced by peripheral conversion of some adrenal hormones, addition of flutamide to orchiectomy provides "total" androgen blockade at the level of the androgen receptor (42). It is, therefore, possible that the negative effects on emotional functioning observed in our study follow from the action of flutamide on androgen receptors in the brain. There is documentation of androgen receptors in the brain from animal studies (43,44). There is also functional evidence for the presence of androgen receptors in the pituitary and perhaps the hypothalamus of humans, based on administration of antiandrogens to normal men. For example, when flutamide (or another antiandrogen) is administered, increases occur in serum luteinizing hormone and testosterone (45-48), and treatment with testosterone suppresses serum luteinizing hormone (49,50).

Less established are the implications of a "total" blockade of androgen receptors for human behavior and whether or not changes in levels of androgens that occur as a result of blocking androgen receptors have any effect on neuropsychiatric systems (37). Our QOL results can only permit speculation as to the mechanism responsible for the compromised emotional functioning of patients receiving antiandrogen treatment. We encourage investigators to broaden the scope of outcome measures used in trials of total androgen blockade treatment and to engage in more basic research capable of addressing mechanisms of antiandrogen drug action on neuropsychiatric outcomes.

Explanations for the worse emotional functioning of patients in the flutamide arm aside, appreciation of the clinical significance of the MHI scores obtained in this trial would be useful. We can do so by comparing our MHI data to MHI scores obtained by the Medical Outcomes Study (51) for patients who had made a visit to a medical provider for the medical condition indicated or, in the case of mental health, for any reason. These normative data are based on the same five-item MHI scale (51) administered to patients in our trial; in all comparisons, higher scores reflect better emotional functioning. At 6 months, the median MHI score for the orchiectomy plus placebo arm was 84, whereas the median MHI score for the orchiectomy plus flutamide arm was 76, eight points lower (worse). For another eight-point difference, consider the median score of 88 observed for patients with two conditions, benign prostatic hyperplasia and hypertension, versus the median score of 80 observed for patients with congestive heart failure (51). These two conditions differ in clinical severity and, as would be expected, MHI scores are lower for patients with congestive heart failure. The emotional functioning of flutamide arm patients at 6 months (median score, 76) was worse than that reported by patients with congestive heart failure (median score, 80) but better than that reported by patients with chronic obstructive pulmonary disease and hypertension (median score, 72). The sensitivity of the MHI

to serious emotional dysfunction is documented by a median score of 44 for patients with clinical depression, a score much lower (worse) than that observed for the patients receiving orchiectomy plus flutamide.

In conclusion, a comprehensive assessment of QOL was prospectively implemented in a double-blind, placebo-controlled, randomized trial of two treatments for patients with stage M₁ carcinoma of the prostate. The high compliance rate and quality of information support the feasibility of QOL assessments in cooperative group trials and indicate that the QOL data can supplement conventional measures of treatment efficacy such as survival. In fact, without a comprehensive QOL measure (i.e., one that measured more than symptom status), we could not have properly evaluated the full scope of treatment effects, both palliative and negative, on patient functioning in this trial. An important contribution of this trial was also the opportunity to evaluate the effect on QOL of androgen-deprivation treatment involving only orchiectomy. A consistent pattern of QOL findings, obtained in a rigorously designed trial, indicates that, during the initial 6 months of protocol treatment, adding flutamide to bilateral orchiectomy does not contribute to the palliative effect of orchiectomy alone for patients with stage M₁ carcinoma of the prostate. In fact, the addition of flutamide resulted in less benefit, particularly with respect to emotional functioning.

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NOTES

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