Quality of Life Impact of Three Different Doses of Suramin in Patients with Metastatic Hormone-Refractory Prostate Carcinoma

Results of Intergroup 0159/Cancer and Leukemia Group B 9480

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BACKGROUND. Research has suggested that men with hormone-refractory prostate carcinoma have a lower quality of life (QOL) compared with men who have hormone-sensitive prostate carcinoma and that quality of life (QOL) steadily declines over the last year of life for men with prostate carcinoma. The primary purpose of the current study was to evaluate whether there was evidence of palliative effects associated with suramin at any of the three doses administered in the original clinical trial.

METHODS. Patients with histologically confirmed advanced hormone-refractory adenocarcinoma of the prostate were randomized to receive suramin at a low dose (n = 129; median age, 69 years), an intermediate dose (n = 129; median age, 71 years), or a high dose (n = 127; median age, 70 years) as part of the Intergroup 0159/Cancer and Leukemia Group B 9480 trial. Patients completed a battery of assessment tools, including the Functional Assessment of Cancer Therapy (FACT)—Prostate, the Center for Epidemiological Studies—Depression Scale (CES—D), the Brief Pain Inventory, and an opioid medication log, at baseline, on Day 1 of the sixth week of active therapy, during the second week after treatment termination, and 3 months after administration of the final suramin dose.

RESULTS. Patients who received low-dose suramin reported improvement in QOL (FACT—General: $P < 0.01$; FACT—Treatment Outcome Index: $P < 0.01$) and decreased levels of depression (CES—D: $P < 0.0006$) during treatment compared with patients in the intermediate- and high-dose arms. After treatment, all groups experienced equal decreases in FACT and CES—D scores.

CONCLUSIONS. The pattern of results suggests that the lowest dose of suramin administered had a palliative effect in terms of improvement in QOL and decreased levels of depression and that this effect was lost once suramin was discontinued. *Cancer* 2004;101:2202–8. © *2004 American Cancer Society.*

KEYWORDS: prostate carcinoma, quality of life, suramin, hormone-refractory adenocarcinoma.

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Prostate carcinoma is one of the most common malignancies and is the second leading cause of cancer-related mortality among men in North America.[1] Once men develop hormone-refractory prostate carcinoma, the median survival period ranges from 12 to 20 months, and no treatment options have been found that significantly prolong survival. The Cancer and Leukemia Group B (CALGB) 9480/Intergroup 0159 trial tested the efficacy and toxicity of three different doses of suramin in men with hormone-refractory prostate carcinoma. That trial revealed no difference among the three treatment arms in terms of overall or progression-free survival, although toxicity was found to be dose dependent, with increasing toxicity being associated with increasing suramin doses.[2]

Research has suggested that men with hormone-refractory prostate carcinoma have a lower quality of life (QOL) compared with men who have hormone-sensitive prostate carcinoma[3] and that QOL steadily declines over the last year of life for men with prostate carcinoma.[4] Therefore, if treatments do not affect survival, an important issue is whether a given treatment has an impact on symptoms or QOL.[5] In another trial, Small et al.[6] demonstrated the palliative effects of suramin plus hydrocortisone compared with hydrocortisone plus placebo, as evidenced by reductions in pain intensity and opioid use. QOL, as measured by the Functional Assessment of Cancer Therapy (FACT), improved slightly in both groups, but no group differences were found. Similar improvements in QOL have been reported in association with other interventions.[7] Therefore, the purpose of the current study was to investigate whether there was evidence of suramin's putative palliative effects at any of the three doses evaluated in the original study.

As a secondary issue, the interpretation of results of QOL studies conducted within the context of multiinstitutional cooperative group studies often is limited by poor accrual to the QOL component of the study. Therefore, the current study used a centralized QOL assessment procedure designed to maximize the amount of QOL data collected.

MATERIALS AND METHODS

Patients with histologically confirmed advanced hormone-refractory adenocarcinoma of the prostate were randomized (after informed consent was obtained) with equal probability to receive suramin at a low dose (total, 3.192 g/m^2), an intermediate dose (total, 5.320 g/m^2), or a high dose (total, 7.661 g/m^2) as part of the CALGB 9480/Intergroup 0159 trial, as has been described previously.[2] All patients received an oral dose of 25 mg hydrocortisone each morning and 15 mg orally each afternoon throughout their treatment with suramin. Patients randomized to the high-dose arm also received 0.1 mg fludrocortisone orally every other day. QOL, depression, and pain were measured at baseline, on Day 1 of the sixth week of active therapy, during the second week after treatment termination, and 3 months after the last dose of suramin was administered. If a patient was removed from study treatment due to toxicity after the 6-week assessment, assessments still were made at the 2-week and 3-month posttreatment time points. If treatment was terminated before the sixth week of active treatment, then the 6-week QOL assessment was skipped, but the

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2-week and 3-month posttreatment assessments still were made.

Baseline QOL data were collected at the time of enrollment at each institution and were required as part of the prerandomization data collection process. The subsequent assessments were centralized through the Center for Psycho-Oncology Research at Dartmouth-Hitchcock Medical Center (Lebanon, NH). QOL questionnaires were mailed at the appropriate follow-up points. Patients were given the option of either completing the questionnaires and giving them to the CRA at their institution to transmit via mail or facsimile to Dartmouth or completing the questionnaires over the phone with a research assistant at Dartmouth who was blind to treatment assignment. This procedure has been used in previous CALGB studies and has been shown to increase data collection levels for both questionnaire-completion methods (i.e., patient completion and telephone completion), yielding equivalent results for both of these approaches.[8]

Functional Assessment of Cancer Therapy—Prostate (FACT—P)

The FACT—General (FACT—G)[9] is a 28-item QOL measure that provides a total score as well as 5 subscale scores: Physical, Functional, Social, Emotional Well-Being, and Satisfaction with Treatment. The FACT—P is a combination of the FACT—G with a 12-item prostate carcinoma subscale that contains items assessing symptoms/problems related to prostate carcinoma and its treatment. The Treatment Outcome Index (FACT—TOI) is derived from the sum of the Physical Well-Being, Functional Well-Being, and Prostate Carcinoma subscale scores and is believed to be the most sensitive measure of patient-reported health. Evidence supports the reliability, validity, and sensitivity of the instrument and its ability to detect change over time.[4] A clinically meaningful change in FACT—G and FACT—TOI results has been defined as a 5–7-point change on either scale.[9,10]

Center for Epidemiological Studies—Depression (CES—D) Scale

The CES—D[11] is a 20-item measure of depressive symptoms that is widely used in epidemiologic studies of depression. Patients are asked to rate how frequently they have experienced each symptom on a 4-point scale ranging from *rarely or none of the time* to *most or all of the time.* The CES—D has been studied extensively and has strong data supporting its validity and reliability.[12]

Brief Pain Inventory (BPI)

The BPI[13] was developed specifically as an instrument to assess cancer-related pain and pain interference. A series of scales ranging from 0 to 10 are used to assess pain at its most intense, at its least intense, on average, and at the time of the survey and to assess how pain interferes with several QOL domains, including activity levels, walking ability, mood, sleep, work, and relationships with others. Patients were also asked to estimate the degree of pain relief, indicate areas of pain on a schematic drawing, and estimate the percentage of pain due to cancer-related versus noncancer-related causes. The BPI has strong evidence supporting its reliability and validity, has been used in a groupwide Eastern Cooperative Oncology Group study that demonstrated its acceptability to patients and its feasibility in clinical trials, and has been adopted by the World Health Organization as a measure of cancer-related pain.[13,14]

Opioid Pain Medication Log

Patients were asked to maintain a log of medications taken for pain in the 3 days before completing their questionnaires. Opioid analgesic doses were converted to morphine equivalents.[15]

Statistical Analysis

For measures that were normally distributed, a piecewise linear random coefficient model was used to examine longitudinal changes over time in QOL within each treatment group. Within this context, a linear model or a straight-line model involving an intercept and slope effect was used to describe QOL during treatment. The piecewise linear model allows the rate of QOL change (slope) to change when treatment ends, resulting in the description of posttreatment QOL by another straight line. The mean QOL at baseline (intercept) is assumed to be equal in all three treatment groups. Two hypotheses—namely, the equality of treatment group slopes during treatment (i.e., the treatment-specific change in QOL response over time during active treatment) and the equality of treatment group slopes posttreatment—were tested within this model.

For measures that were not normally distributed, the area under the curve (AUC) during treatment was estimated for each patient. The average for each measure during treatment/posttreatment was computed as the ratio of AUC to the length of the treatment/posttreatment interval. The Kruskal–Wallis test was used to compare treatment groups.

Patient registration and statistical analyses were

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)		
	Low dose (n = 129)	Intermediate dose (n = 129)	High dose (n = 127)
Median age (range) in yrs	69 (41–84)	71 (44–85)	70 (40–84)
Race/ethnicity			
White	106 (82)	111 (86)	94 (74)
Hispanic	2 (2)	3 (2)	5 (4)
Black	20 (15)	14 (11)	26 (20)
Other	1 (1)	1 (1)	2 (2)
Performance status			
0	47 (36)	54 (42)	55 (43)
1	66 (51)	58 (45)	57 (45)
2	16 (12)	17 (13)	15 (12)
Histologic grade of tumor			
Well differentiated (Gleason 4)	16 (12)	8 (5)	17 (13)
Moderately differentiated (Gleason 5–7)	50 (39)	59 (46)	54 (43)
Poorly differentiated or undifferentiated (Gleason 8–10)	55 (42)	57 (44)	44 (35)
Missing or unknown	8 (6)	7 (5)	12 (9)
Disease site			
Bone only	74 (57)	74 (57)	74 (58)
Soft tissue	55 (43)	55 (43)	53 (42)

conducted by the CALGB Statistical Center at Duke University (Durham, NC).

RESULTS

Of the 390 patients enrolled in the treatment trial, 385 (98.7%) were enrolled in the QOL component at baseline: 129 in the low-dose arm, 129 in the intermediate-dose arm, and 127 in the high-dose arm. In addition, > 90% of data were collected at follow-up assessment for patients who remained in the study. Table 1 summarizes basic demographic characteristics by treatment group. Patients were generally Caucasian (81%), with a median age of 70 years (range, 40–85 years). The majority of patients (88%) had a performance status score of 0 or 1. Most patients had moderately (42%) or poorly differentiated (41%) tumors, and the sample was approximately evenly divided between patients with bone-only disease (58%) and patients with soft tissue disease (42%).

In the original trial, 64% of patients completed treatment. Therefore, the analysis of psychosocial data is complicated by early treatment termination. To examine the impact of early termination, analyses were stratified according to whether treatment was terminated prematurely. Parameters describing strata and interactions between slopes and strata were incorporated into the model. Of primary interest was whether treatment differences (i.e., differences in slope) were consistent across strata. Because no evidence of a significant interaction was found, data from patients who completed treatment and data from patients who did not were combined.

Analysis of the two primary summary measures of the FACT (i.e., the FACT—G and the FACT—TOI) using the piecewise linear random coefficient model revealed that during treatment, patients in the low-dose arm experienced improvements in both summary scores (FACT—G: $P < 0.01$; FACT—TOI: $P < 0.01$), patients in the intermediate-dose arm exhibited no change from baseline, and patients in the high-dose arm experienced decreases in both scores (FACT—G: $P < 0.001$; FACT—TOI: $P < 0.001$; Table 2). After the termination of treatment, scores on both scales declined at the same rate in all three groups. Examination of the subscale scores revealed that during treatment, patients in the low- and intermediate-dose arms exhibited significant improvements on the Emotional Well-Being (low-dose arm: $P < 0.001$; intermediate-dose arm: $P < 0.05$) and Prostate Additional Concerns (low-dose arm: $P < 0.001$; intermediate-dose arm: $P < 0.05$) subscales, while patients in the low-dose arm exhibited significant improvements on the Physical Well-Being ($P < 0.05$) and Functional Well-Being subscales ($P < 0.05$). After treatment, all three groups experienced equal declines in subscale scores. No significant changes were documented during or after treatment on the Social or Family Well-Being subscales.

Cella et al.[10] demonstrated that 5–7-point changes on the FACT—G and FACT—TOI scales are clinically

TABLE 2
Mean Scores, Standard Errors, and Sample Sizes for the FACT—G and FACT—TOI at Each Assessment

	Mean Score (SD)			
	Baseline	Mid-Tx (Week 6)	2 weeks post-Tx	3 mos post-Tx
FACT—G[a]				
Low	90.3 (1.3)	95.7 (1.32)	89.8 (1.7)	89.3 (1.9)
Intermediate	84.7 (1.5)	90.7 (1.6)	81.4 (1.9)	80.7 (2.1)
High	88.2 (1.6)	85.4 (1.7)	76.9 (1.8)	78.8 (2.3)
FACT—TOI[a]				
Low	72.1 (1.5)	77.7 (1.4)	71.1 (1.9)	70.9 (2.0)
Intermediate	64.4 (1.5)	71.8 (1.4)	62.0 (2.0)	60.2 (2.0)
High	68.8 (1.6)	65.9 (2.0)	56.7 (1.9)	58.4 (2.4)
Physical Well-Being				
Low	22.1 (0.48)	23.3 (0.41)	21.4 (0.57)	21.1 (0.62)
Intermediate	20.4 (0.52)	21.6 (0.45)	17.9 (0.65)	17.9 (0.64)
High	21.4 (0.51)	19.6 (0.61)	16.2 (0.67)	17.0 (0.73)
Social and Family Well-Being				
Low	23.7 (0.40)	24.8 (0.39)	24.1 (0.41)	24.5 (0.41)
Intermediate	23.7 (0.40)	24.1 (0.45)	23.4 (0.47)	24.0 (0.48)
High	23.6 (0.43)	23.9 (0.43)	23.9 (0.37)	24.0 (0.47)
Emotional Well-Being				
Low	18.2 (0.45)	19.9 (0.40)	18.7 (0.46)	18.4 (0.52)
Intermediate	17.3 (0.43)	19.1 (0.42)	17.6 (0.53)	17.3 (0.55)
High	17.6 (0.46)	18.5 (0.48)	17.1 (0.51)	17.0 (0.62)
Functional Well-Being				
Low	19.0 (0.55)	20.4 (0.55)	18.6 (0.65)	18.2 (0.75)
Intermediate	16.3 (0.66)	18.8 (0.60)	15.6 (0.72)	14.9 (0.79)
High	18.7 (0.63)	16.5 (0.70)	13.5 (0.71)	14.4 (0.87)
Prostate Additional Concerns				
Low	31.0 (0.74)	34.0 (0.70)	31.0 (0.89)	31.7 (0.86)
Intermediate	27.7 (0.72)	31.2 (0.68)	28.5 (0.84)	27.4 (0.81)
High	28.9 (0.78)	29.6 (0.94)	26.8 (0.88)	27.0 (1.05)
CES—D[b]				
Low	25.7 (0.71)	24.4 (0.73)	26.8 (1.01)	26.1 (0.90)
Intermediate	28.8 (0.71)	26.9 (0.83)	31.0 (1.05)	30.5 (1.16)
High	27.5 (0.82)	30.2 (1.16)	33.2 (1.05)	32.9 (1.31)

FACT—G: Functional Assessment of Cancer Therapy—General; FACT—TOI: Functional Assessment of Cancer Therapy—Treatment Outcome Index; SD: standard deviation; CES—D: Center for Epidemiologic Studies—Depression; Tx: treatment.

[a] Sample sizes by dose and time point for the FACT: low-dose: baseline = 116, mid-Tx = 103, 2 weeks post-Tx = 110, 3 months post-Tx = 90, Intermediate-dose: baseline = 113, mid-Tx = 90, 2 weeks post-Tx = 97, 3 months post-Tx = 82; high-dose: baseline = 113, mid-Tx = 87, 2 weeks post-Tx = 99, 3 months post-Tx = 72.

[b] Sample sizes by dose and time point for the CES—D: low-dose: baseline = 98, mid-Tx = 86, 2 weeks post-Tx = 89, 3 months post-Tx = 79, Intermediate-dose: baseline = 98, mid-Tx = 74, 2 weeks post-Tx = 79, 3 months post-Tx = 74; high-dose: baseline = 101, mid-Tx = 70, 2 weeks post-Tx = 87, 3 months post-Tx = 65.

significant. Examination of the mean values presented in Table 2 reveals that for patients in the low-dose group, FACT—G and FACT—TOI scores improved between baseline and 6-week follow-up by 5.4 and 5.7 points, respectively. Similar levels of change on these scales were documented in patients in the intermediate-dose arm. However, interpretation of these findings must be tempered by knowledge of the differential dropout rate between the low-dose (10%) and intermediate-dose arms (21%) before the sixth week of treatment, primarily due to increased toxicity in the latter group. That is, the mean for the intermediate group may be somewhat inflated, because patients experiencing more severe toxicity (who thus would have poor QOL scores) were more likely to be withdrawn from the study. Therefore, apparent improvements in the intermediate-dose group during treatment must be interpreted with caution, particularly because the analysis described above, which uses all available data to estimate scores for patients who discontinued treatment, suggests that patients in the intermediate-dose group did not experience improvements in FACT—G or FACT—TOI scores during treatment.

Similar analyses involving the CES—D revealed no differences among treatment arms in terms of the rate of change during treatment or the rate of change post-treatment. However, because of the observed skew-

ness of CES—D scores in the current study, the AUC method was used to analyze the average daily CES—D score during treatment. The distribution of average daily CES—D scores during treatment was significantly different among the three treatment arms ($P = 0.0006$), with patients in the low-dose arm having lower Depression scale scores. However, as in our analysis of FACT data, posttreatment CES—D scores decreased at a similar rate across all groups.

Examination of the BPI revealed that 66% of patients reported pain at the baseline assessment. Analyses of the worst pain and pain interference scores on the BPI and of data from opioid medication logs revealed no group differences during or after treatment when the entire sample was considered, and these group differences continued to be absent when only patients reporting pain at baseline were considered.

DISCUSSION

The CALGB 9480 clinical trial did not uncover a dose-response relation between suramin and overall or progression-free survival. However, there was a significant dose-response relation between suramin use and toxicity, with patients in the low-dose arm experiencing the least severe toxicity.[2] Data from the FACT and the CES—D revealed similar findings—i.e., patients in the low-dose arm had the highest QOL and the lowest levels of depression. The pattern of QOL and depression scores is intriguing, as these measures improved during treatment for patients in the low-dose arm. These improvements not only were statistically significant but also reached a level that has been considered clinically significant in other research.[10] These results are of particular interest, because the observed improvements in QOL occurred despite the finding that low-dose suramin remains associated with some amount of toxicity (e.g., 18% of patients in the low-dose arm experienced Grade 3/4 neurotoxicity). Finally, objective response rates (9%, 7%, and 15%, respectively) and prostate-specific antigen response rates (24%, 28%, and 34%, respectively) were lowest in the low-dose arm as compared to the high-dose arm. Because of the study design, a placebo effect (i.e., treatment activity in association with a relatively less toxic dose) cannot be definitively ruled out. However, the pattern of results suggests that patients in the low-dose arm may have experienced palliative effects due to treatment with suramin. Although the mechanism underlying the potential palliative effects of suramin cannot be specified from these data, examination of FACT subscale scores suggests that there was a reduction in physical symptoms, along with improvements in functional and emotional well-being, in the low-dose group.

Further evidence for the palliative effect of suramin can be seen in the posttreatment pattern of results. For example, QOL scores declined at a similar rate across all three groups once suramin was discontinued. Nonetheless, examination of Table 2 reveals that patients in the low-dose arm continued to have higher QOL scores at the 3-month posttreatment assessment.

The one inconsistent finding in the current study was the lack of evidence of pain reduction or opioid use. However, this negative finding may have been related to significant differences in design between the two studies. A previous Phase III trial of suramin[6] included only patients who had painful bone metastases for which stable and chronic opioid analgesic–based treatment was necessary, whereas there were no inclusion criteria related to pain or opioid use in the current study. This difference in eligibility requirements may have resulted in significant disparities with respect to a variety of important clinical parameters. In addition, given that in the current study only 66% of patients reported any level of pain at baseline and that only 35% were taking opioids at baseline (20% regularly and 15% occasionally), the current study may not have had sufficient power to adequately evaluate dose-response differences in pain intensity and/or opioid intake.

The data collection method used in the current study also is noteworthy. Accrual and collection of follow-up QOL data are major problems in large-scale multicenter cooperative studies. In the current study, QOL data collection was centrally coordinated. Patients were tracked by Dartmouth personnel, and QOL questionnaires were mailed at the appropriate times. Patients were offered the option of either completing the questionnaires and giving them to their institution's CRA to be transmitted by mail or facsimile to Dartmouth or completing the questionnaires via phone with a research assistant at Dartmouth. This method resulted in the collection of > 90% of the data for patients who remained in the study, demonstrating that high response rates for QOL data collection can be achieved in cooperative trials.

The development of novel active therapeutic agents for the treatment of hormone-refractory prostate carcinoma remains a high priority. The current study serves as a model for the integration of QOL evaluation into such studies. Although the primary goal of Phase III treatment trials will continue to be the prolongation of survival, the careful analysis of QOL in large multicenter trials will be critical when 1) the agents being tested have significant toxicities associated with them (particularly when such agents have the potential for only a small incremental im-

provement in survival) or 2) there is evidence suggesting that the agents being tested possess palliative activity.

In summary, the original clinical trial of suramin did not demonstrate a dose-response relation with overall or progression-free survival, although toxicity was found to increase with increasing doses. It is noteworthy that patients in the low-dose arm reported improved QOL (as measured using the FACT), with these improvements reaching levels considered to be clinically meaningful. Similarly, during the course of treatment, depression scores were lower in the low-dose arm compared with the intermediate- and high-dose arms. Overall, in the current study, low-dose suramin appeared to be associated with clinically meaningful improvements in QOL during therapy. Suramin appears to be unlikely to be further developed for the treatment of men with hormone-refractory prostate carcinoma, given the development of an entirely new generation of cytotoxic agents. Nonetheless, the apparent palliative effects of suramin are of interest, despite the absence of evidence of a dose-dependent survival advantage yielded by this agent. Furthermore, our results indicate that the careful analysis of QOL is both feasible and warranted in large multicenter trials of treatment regimens for hormone-refractory prostate carcinoma.

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