COMMUNICATION

Vinorelbine, Doxorubicin, and Prednisone in Androgen-Independent Prostate Cancer

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BACKGROUND. Ultimately, patients with metastatic prostate cancer progress on androgen ablation therapy. The investigation of new chemotherapeutic regimens for the treatment of androgen-independent prostate cancer (AIPC) is essential. The authors conducted a Phase II trial with vinorelbine, doxorubicin, and daily prednisone (NAP) to investigate the antitumor activity and palliative response of this regimen in patients with AIPC.

METHODS. Forty-six patients entered this Phase II combination chemotherapy trial. Patients were treated with both vinorelbine and doxorubicin at doses of 20 mg/m^2 on Days 1, 8, and 15 every 28 days and prednisone 5 mg twice daily. Endpoints included prostate-specific antigen (PSA) response and palliation, as measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) instrument, the Brief Pain Inventory Scale, and a narcotic analgesic log.

RESULTS. The median follow-up for all 46 patients was 13.4 months. Fifty-two percent of patients had impaired performance status at baseline. One responding patient remained on NAP and was progression-free at 11.5 months. Thirty-nine patients progressed, 3 patients died prior to response assessment, and 3 patients refused therapy. The median overall survival was 57 weeks (95% confidence interval [95% CI], 36–76 weeks), and the median time to disease progression was 17 weeks (range, 11–24 weeks). The PSA response among the 36 patients who completed 3 cycles of NAP was 42% (95% CI, 26–59%). There was a statistically significant improvement in quality of life measured both by the FACT-General instrument ($P = .03$) and the FACT-P instrument ($P = .0006$) over the 3 months compared with baseline measurements. Pain medicine use also improved: The median morphine equivalents among patients who were taking pain medications at the time of study enrollment showed a substantial decline after 1 cycle of treatment that was maintained. Pain (as assessed by the Brief Pain

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Inventory) improved compared with baseline pain at the 2nd-month assessment (worst pain, P = .08; least pain, P = .02; and average pain, P = .003). Overall, the regimen was tolerated well. The most common side effects were mild fatigue and gastrointestinal complaints (all of which were Grade 1 or 2 [according to Version 2.0 of the Expanded Common Toxicity Criteria]). Seventeen patients (37%) experienced Grade 3 or 4 neutropenia. Five patients (11%) developed a cardiac ejection fraction of <50% during treatment and had doxorubicin discontinued. No patients developed clinical congestive heart failure.

CONCLUSIONS. The NAP combination produced substantive palliation and a moderate response rate in men with AIPC. ***Cancer*** **2006;107:1093–100.** © *2006 American Cancer Society.*

KEYWORDS: prostate cancer, chemotherapy, androgen-independent prostate cancer, quality of life, hormone-refractory prostate cancer, analgesic scale.

Prostate cancer is the most common malignancy of the urinary tract. It is estimated to account for >234,000 new diagnoses and 27,350 deaths in 2006.[1] Approximately 30% to 50% of patients with prostate cancer will have metastases at some time during the course of their disease.[2] Blockade of testicular androgens with bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists achieves temporary tumor control or regression in 80% to 95% of patients.[3,4] These therapies result in a median progression-free survival of 12 months to 18 months and an overall survival between 24 months and 30 months.[5,6]

Ultimately, virtually all patients with metastatic disease progress on androgen ablation therapy. The treatment of patients who have androgen-independent prostate cancer (AIPC) with chemotherapy, either as a single agent or in combination, has resulted in response rates of bidimensional, measurable disease of 20% to 50% and prostate-specific antigen (PSA) response rates of 30% to 70% and greater. Thus, a number of agents have shown reproducible activity in patients with metastatic, hormone-refractory prostate cancer. Recently, taxotere-based studies confirmed a prolongation of survival with chemotherapy.[7,8] Such improvements in chemotherapy in recent years have been accompanied by substantial chemotherapeutic-induced toxicity. Thus, the balance of responses and toxicity remains a critical issue for treating physicians. Nonetheless, quality-of-life issues have not been assessed for many widely used chemotherapeutic regimens. Vinorelbine tartrate is a semisynthetic vinca alkaloid that interferes with microtubule assembly. Clinical response rates to vinorelbine tartrate in patients with prostate cancer have ranged from 13% to 17% in single-agent studies.[9–11] Combinations of vinorelbine with other chemotherapeutics, such as estramustine, have achieve response rates from 24% to 71%.[12,13] Various combinations of vinorelbine and prednisone also have been reported. In a recent Phase II trial of vinorelbine and prednisone, a >50% PSA response rate was observed in 36% of patients, and pain reduction was observed in 44% of patients.[14] Similar responses and the suggestion of a favorable toxicity profile were reported from a second Phase II trial of the same regimen.[15]

It has been demonstrated that doxorubicin is effective as a single agent and in many combination chemotherapy regimens for the treatment of prostate cancer. In early Phase II Southwest Oncology Group trials, it was observed that doxorubicin had a dose-response relation in prostate cancer.[16] In a randomized study that was conducted by the Eastern Cooperative Oncology Group (ECOG), doxorubicin at a dose of 60 mg/m^2 was superior to 5-fluorouracil, with a 25% (vs. 5%) partial response rate.[17] Early clinical trials of weekly doses of doxorubicin revealed promising responses.[18] More recent combination regimens that include doxorubicin also have shown activity in 46% to 58% of patients.[19,20]

Doxorubicin administered weekly in doses that achieve dose intensity similar to that achieved with traditional 3-weekly schedules produces responses in soft tissue, bone, and visceral sites of disease and is associated with substantially reduced acute toxicity, increased Karnofsky performance scores, and increased palliative responses in bone pain.[18,21–23] Cardiotoxicity also is reduced substantially.[24,25] Furthermore, the results from a randomized trial that compared doxorubicin plus prednisone with prednisone alone suggested improved subjective response and longer duration of stable disease in the doxorubicin and prednisone group.[26] Thus, doxorubicin administered on a weekly schedule provides an opportunity to exploit the efficacy of doxorubicin while limiting potential toxicity.

Glucocorticoids have been reported in the treatment of advanced prostate cancer since the 1950s.[27] Tannock et al. reported improvement in pain in 38%

of patients who received daily prednisone and observed that pain reduction was associated with improved quality of life.[28] Other studies have confirmed the significant palliative and quality-of-life benefits of prednisone.[29,30] Single-agent PSA responses of >50% have been reported in 21% to 24% of patients in Phase III trials for prednisone.[30–32] The treatment of AIPC with low-dose prednisone has resulted in symptomatic improvement in 30% of patients, producing prolonged pain relief in a few patients and transient relief in others.[28] Prednisone at this dose has limited toxicity and has been a useful adjunct to other chemotherapeutic regimens, such as combinations that include mitoxantrone.

The investigation of new chemotherapeutic regimens for the treatment of AIPC is essential. There clearly is room for improvement. In addition to the traditional evaluations of response rate and duration, endpoints such as symptom palliation and quality of life contribute to the overall assessment of the benefits and risks of therapy. We conducted a Phase II trial with vinorelbine, doxorubicin, and daily prednisone (NAP) to examine the clinical efficacy and quality-of-life improvement for patients with advanced AIPC.

MATERIALS AND METHODS

Eligibility

Patients with histologically documented AIPC were enrolled under an Institutional Review Board-approved protocol. AIPC was defined as failure of hormone therapy (either gonadotropin-releasing hormone analog or orchiectomy) and antiandrogen withdrawal, manifested by at least 1 of the following: rising PSA, new bone disease, or new soft tissue disease. Patients could have additional secondary hormone manipulations; however, no new hormone therapy was permitted within 4 weeks of enrollment. Prior radiation therapy or surgery was permitted, but not within 1 weeks and 4 weeks of enrollment, respectively. No prior immunotherapy, therapeutic radiopharmaceuticals, or chemotherapy was permitted.

Patients were required to have an ECOG performance status of 0 or 1 and a life expectancy $\geq$3 months. Patients were required to have adequate renal function (creatinine, $\leq$2.0 μmol/L), liver function (bilirubin $\leq$2.0 μmol/L) hematologic function (granulocytes $\geq$1000/μL, platelet count $\geq$100,000/μL, and hemoglobin $\geq$10 g/dL), and cardiac function (ejection fraction $\geq$50%). Patients who had a history of another malignancy within 5 years, known brain metastases, active uncontrolled infection, or psychiatric or other illness that precluded appropriate informed consent were excluded.

Treatment Plan

This was a single-arm, Phase II trial. After signed informed consent, baseline studies were obtained that included PSA evaluations, bone scans, chest X-rays, multiple-gated acquisition (MUGA) scans, and several quality-of-life instruments: the Functional Assessment of Cancer Therapy-Prostate (FACT-P) assessment (which includes the FACT-General [FACT-G] instrument), the Brief Pain Inventory (BPI), and the Narcotic Pain Medication Logbook. Computerized tomography (CT) and magnetic resonance imaging (MRI) were performed when clinically indicated but were not required. Patients received NAP on the following schedule: vinorelbine tartrate (Navelbine®; Glaxo-Smith-Kline-Welcome, Research Triangle Park, NC) at a dose of 20 mg/m^2 every week for 3 weeks every 4 weeks, doxorubicin at a dose of 20 mg/m^2 every week for 3 weeks every 4 weeks, and oral prednisone at a dose of 5 mg twice daily.

Evaluation

The primary endpoints for the study were response, time to progression (defined as the time from study entry to progression at any site, including PSA), and survival. Quality of life was evaluated by using the FACT-G and FACT-P subscales, the BPI scale, and the Narcotic Pain Medication Logbook.

After 3 cycles of NAP (or with clinical evidence of disease progression) patients were reevaluated with PSA evaluations, chest X-rays, and bone scans. CT and MRI studies were obtained if they were indicated clinically. The primary response endpoint was PSA. A partial response (PR) was defined as a decrease >50% in PSA from baseline confirmed with a second PSA determination at the next visit in patients without bone scan progression; a complete PSA response (CR) was defined as a normalization of PSA level, bone scan, and other measurable sites of disease. Progressive disease (PD) was defined as an increase >50% in the PSA level from PSA nadir. Patients with stable or responding disease were continued on therapy. Patients were removed from study for disease progression or unacceptable toxicity. Patients were followed until death. Three cycles of NAP were considered adequate therapy. No patient was considered nonevaluable because of early death or progression.

Quality of life was assessed by using the FACT-P (FACT-G and FACT-P subscales) at baseline, after the 2nd and 3rd cycle of NAP and 1 month after completing the 3rd cycle of therapy. The BPI form and the Narcotic Pain Medication Logbook were completed at baseline and at the end of each 3-week cycle. From the pain logbook, morphine equivalents for narcotic pain medicines were calculated as described previously.[33]

TABLE 1
Pretreatment Patient Characteristics

Characteristic	No. of patients (%)
No. enrolled	46
Median age (range), y	68 (50–82)
ECOG performance status	
0	22
1	24
Race	
White	34 (74)
African-American	12 (26)
PSA (ng/mL)	
Median	144
Mean	395
Range	9–4379
Cardiac ejection fraction (%)	
Median	61
Mean	62

ECOG indicates Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Toxicity was graded according to the Expanded Common Toxicity Criteria version 2.0. Dose modification for vinorelbine tartrate and doxorubicin was permitted. Supportive measures were permitted, including the use of blood transfusions and blood products as well as growth factors, according to the American Society for Clinical Oncology guidelines. Palliative radiation was not permitted while patients were on protocol.

Statistical Analysis

Kaplan–Meier methods were used to calculate time to event medians and confidence intervals. To account for the correlation of measurements within individuals, mixed-model regression was used to analyze the longitudinal FACT-G and FACT-P scores. Estimated means were calculated first by grouping measurements into baseline, 1-month, 2-month, and 3-month categories. Reported *P* values and average increases per month were derived from regression analyses by using the actual date of collection as a continuous variable. The BPI response changes from baseline to Month 3 were analyzed with Student *t* tests for paired data.

RESULTS

Between 1998 and 2002, 46 patients with hormone-refractory prostate cancer were enrolled at the Wake Forest University Heath Sciences Comprehensive Cancer Center. Patient characteristics at baseline are outlined in Table 1. All but 2 patients had evidence for bony metastases on baseline bone scans. Twenty-four patients (52%) had compromise of functional status (an ECOG performance status of 1) at study entry. Therapy prior to study entry is shown in Table 2.

TABLE 2
Prior Therapy

	No. of patients
Prostatectomy	20
Radiation therapy	21
Cryosurgery	1
Orchiectomy	17
Lupron/Zoladex	28
Antiandrogens	38
Ketoconozale/steroid	6
Cytadren	1
PC-SPES*	1
Bisphosphonates	4

* PC-SPES is an herbal prostate cancer product.

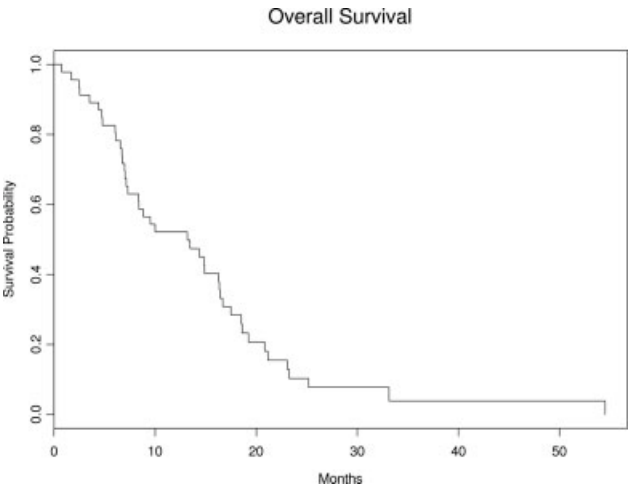

FIGURE 1. Overall survival is illustrated.

The median follow-up for all 46 patients was 13.4 months. At the time of last follow-up, 1 patient remained on NAP and was progression free at 11.5 months. The median overall survival was 57 weeks (95% confidence interval [95% CI], 36–76 weeks) (see Fig. 1). Thirty-nine patients had PD with a median time to disease progression of 17 weeks (range, 11–24 weeks). Relapse occurred most frequently in PSA and bone, but progression at multiple sites was common (Table 3). Three patients died prior to restaging, and 3 patients refused further therapy.

The majority of patients completed 3 cycles of NAP (see Table 4). The response among the 36 patients who completed 3 cycles of NAP is outlined in Table 5. Using PSA criteria, the PR rate was 42% (95% CI, 26–59%), and the a median time to PR was 7 weeks (range, 3–39 weeks).

Quality of life was measured at baseline and monthly for the first 3 months of treatment. The

TABLE 3
Sites of Progression in 39 Patients

Progression type	No. of patients
Prostate-specific antigen	28
Bone scan/bone X-ray	18
Computed tomography/magnetic resonance image	7
Other	6

TABLE 4
Treatment Duration

No. of cycles completed	No. of patients (%)
3	36 (78.3)
6	21 (45.7)
9	9 (19.6)
12	5 (10.9)

TABLE 5
Prostate-Specific Antigen Response among the 36 Patients who Completed 3 Cycles of Vinorelbine, Doxorubicin, and Daily Prednisone

Maximum PSA decrease	No. of patients (%)
≥50%	15 (42)
25–50%	9 (25)
0–25%	5 (14)
No nadir	6 (17)
Nonevaluable	1 (3)

PSA indicates prostate-specific antigen.

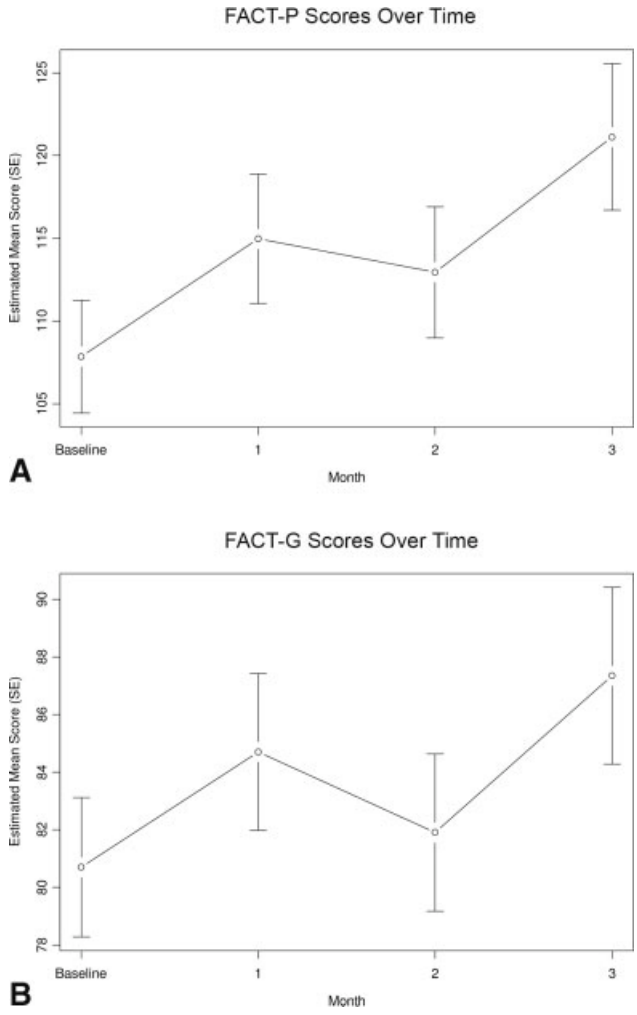

FIGURE 2. (A) Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores and (B) Functional Assessment of Cancer Therapy-General (FACT-G) scores.

overall FACT-P and FACT-G scores are illustrated in Figure 2. There was a statistically significant improvement in both the FACT-G score ($P = .03$), which increased an average of 1.2 points per month, and the FACT-P score, which increased an average of 2.8 points per month ($P = .0006$), over the 3 months compared with baseline scores. These improvements in the FACT-P and FACT-G scores were not the result of a few outliers with large changes in scores: changes in both scores were distributed normally (Fig. 3).

Pain medicine use improved concomitantly with these quality-of-life improvements: the median morphine equivalents among the patients who were taking narcotic pain medications at the time of study enrollment (see Table 6) showed a substantial decline. A 3rd measure of quality of life, the BPI, which measures pain experienced within 24 hours of administration of the questionnaire, also showed improvement (Table 7). Furthermore, there was a strong correlation among pain measurements both at baseline and after treatment. For example, the BPI assessment of worst pain in the last 24 hours and average pain in the last 24 hours correlated with the "significant pain" question in the FACT questionnaire at baseline ($P < .001$ for worst pain; $P < .001$ for average pain). These same BPI and FACT measurements also correlated with the change of pain during treatment. For all patients, the correlation between BPI was significant, ($P < .001$ for worse pain; $P = .005$ for average pain), as it was for the subset of patients who had substantial pain at baseline ($P = .004$ for worst pain; $P = .009$ for average pain).

All 46 patients received treatment and were evaluable for toxicity. In total, 261 cycles were administered. The median number of cycles per patient was 4 (range, 1–16 cycles). Thirty-six patients (78%) completed ≥3 cycles, and 11 patients (24%) received at least 9 cycles (see Table 2). Neutropenia was common but manageable (see Table 8). Grade 4 neutro-

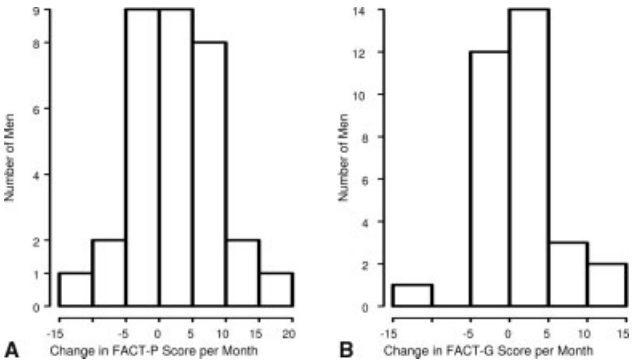

FIGURE 3. These charts illustrate the distribution of changes in (A) Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores and (B) Functional Assessment of Cancer Therapy-General (FACT-G) scores.

TABLE 6
Pain Medication Use among Patients Taking Pain Medication at Baseline

Cycle	No. of patients	Morphine equivalents: Median (Range)	Proportion with 0 Morphine equivalents (%)
Baseline	22	214 (5–2760)	—
Cycle 1	20	60 (0–6885)	30
Cycle 2	16	122 (0–4005)	31
Cycle 3	14	184 (0–2630)	29

TABLE 7
The Brief Pain Inventory

Type of pain	Baseline score	Nadir average score	Decrease (%)	Nadir (Cycle)
Worst pain	3.53	2.62	26	1
Least pain	2.15	1.25	42	2
Average pain	3.16	2.11	33	2

penia (absolute neutrophil count [ANC] $<500 \times 10^6$/L) occurred in 6 patients (13%). Three of those patients required hospital admission for antibiotics. For 1 patient, neutropenia was a factor in the decision for removal from the trial. Severe thrombocytopenia (Table 8) was distinctly uncommon. Ten patients (22%) experienced Grade 3 hyperglycemia (glucose, 250–500 mg/100 mL), and 1 patient (2%) experienced Grade 4 hyperglycemia (glucose, >500 mg/100 mL) while receiving treatment. The majority of these patients had preexisting diabetes. Management usually was achieved with oral medications, although 1 patient discontinued prednisone because of persistently elevated blood glucose.

TABLE 8
Patients with Myelotoxicity

Grade	No. of patients: Platelets: After 3 cycles	Platelets: Maximum toxicity	Absolute neutrophil count: After 3 cycles	Absolute neutrophil count: Maximum toxicity
1	12	22	6	7
2	0	0	10	11
3	0	1	6	11
4	0	0	6	6

Three patients experienced pulmonary emboli, which were fatal in 2 patients, and 2 patients died of acute myocardial infarction as a result. It was unclear whether these events were related to treatment, although these are not known toxicities of the constituents of the NAP regimen.

Other Grade 3 or 4 nonhematologic toxicity included 1 patient with facial swelling and stridor immediately after completion of the doxorubicin and vinorelbine infusion that resolved completely on treatment with corticosteroids and epinephrine. Other toxicities included deep venous thrombosis (1 patient), dyspnea (3 patients), elevated liver function tests (2 patients), fatigue (1 patient), depression (1 patient), and anorexia (1 patient). Five patients (11%) developed a cardiac ejection fraction <50% during treatment (ejection fraction [%] by MUGA = 44%, 49%, 46%, 48%, 48%) and had doxorubicin discontinued at cumulative doses of 336 mg/m^2, 239 mg/m^2, 750 mg/m^2, 140 mg/m^2, and 482 mg/m^2, respectively. These patients remained asymptomatic, and no patients developed congestive heart failure. One patient discontinued treatment because of parasthesias after 12 cycles of treatment. Two patients had episodes of bleeding, including 1 subdural hematoma and 1 gastrointestinal bleed. Both patients were on anticoagulation and had normal platelet counts at the time of those episodes.

Grade 1 and 2 adverse effects included mild fatigue and gastrointestinal toxicity. Twenty-eight patients (61%) experienced Grade 1 or 2 fatigue. Twenty-two patients (48%) experienced Grade 1 or 2 nausea or emesis, 13 patients (28%) experienced Grade 1 or 2 anorexia, and 9 patients (20%) developed Grade 1 or 2 diarrhea.

DISCUSSION

Although substantial strides have been made in the treatment of patients with AIPC, it remains a substantial challenge for physicians to delay the progression of disease and alleviate the symptoms of

metastases. These symptoms include not only bone pain from metastases but also cachexia, fatigue, and malaise. The timing of the introduction of chemotherapy for these patients requires great clinical skill, because maintaining and improving quality of life also means avoiding or limiting treatment-related toxicities, which have increased along with responses to chemotherapy in patients with AIPC. In this article, we have reported on the evaluation of a regimen that was designed to have a modest toxicity spectrum, adequate antitumor response, and limited interference with quality of life. We also explored the utility and feasibility of careful quality-of-life assessments in a Phase II trial.

A noteworthy finding in the study was that treatment with NAP resulted in substantially improved quality-of-life measurements in patients with AIPC. Assessment was carried out with the FACT-G and FACT-P scales, the BPI scale, and a detailed patient log of narcotic use. The FACT scales showed substantial improvement; the FACT-P, which includes the FACT-G and FACT-P subscales, increased an average of 2.8 points per month. Although the FACT is the most widely used quality-of-life indicator in cancer treatment evaluations, the improvements in FACT scores were accompanied by other independent measurements of quality-of-life improvement, including the BPI scale, which measures pain in the last 24 hours (see Table 6) and, thus, provides complementary information to the quality-of-life indicators in prostate cancer. In addition, the direct assessment medication log for pain medicine use corroborated and paralleled the quality-of-life measurements (Table 5).

To our knowledge, the current study is among the few studies and is the only Phase II study in patients with AIPC that has evaluated in detail the quality-of-life impact of chemotherapy. Our results should help other investigators benchmark their Phase II trials to these important endpoints.

Another finding was the rapidity of responses in many patients, both pain responses (Table 5) and decrement of PSA. Thus, although clinical trials in prostate cancer often measure response at 12 weeks, among the patients who eventually responded, 33% responded within the 1st month with decreased PSA levels, and 73% responded in 2 months. In those patients in whom pain was palliated, it occurred rapidly and paralleled the PSA responses (see below). In examining pain medication use, in those patients who were pain medicines at baseline, 30% were completely off pain medicines by the end of the 1st cycle, and this 30% persisted throughout the study, suggesting that, for most patients, improvement will occur early if it is going to occur at all.

The characteristics of patients in the current study were similar to those reported from other trials in patients with AIPC. Of the 46 evaluable patients, $<50\%$ had an ECOG performance status of 0. The median PSA was 395 ng/mL. A substantial cohort of patients was maintained on treatment for a relatively long period. Twenty-one of 46 patients completed at least 6 4-weekly cycles of chemotherapy, and 15 of 46 patients completed ≥ 9 cycles. The PSA response rate observed in this study of (42%) paralleled reports of other studies of in patients with AIPC, particularly in those few Phase II studies that included >40 patients.

Toxicity was modest and manageable. ANC Grade 3 toxicity occurred in only 27 of 261 cycles administered (10%), and ANC Grade 4 in occurred in only 4% of cycles. There were only 2 episodes of neutropenic fever. The only other treatment-related toxicity that occurred frequently was hyperglycemia caused by prednisone, which was controlled easily in all patients.

We showed previously that cardiotoxicity was attenuated markedly by weekly administration of doxorubicin. Clinical congestive heart failure was not observed in the current trial, in keeping with previous reports.[25] Five patients had ejection fractions that fell to just less than 50%, but none developed congestive heart failure.

Overall, the NAP combination chemotherapy regimen was developed prior to reports of increased responses and survival with combinations that included taxotere. The response rate in this clinical trial, as best as can be judged best from nonrandomized trials, probably is inferior to that produced with taxotere-based combinations. However, the tolerability of the regimen and the substantitive palliative response, as defined by 3 standard quality-of-life measures, was noteworthy. We observed that such quality-of-life assessment is relatively easy to incorporate into Phase II trials and provides an important yet rarely obtained insight into palliative effectiveness in a Phase II trial.

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