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A RANDOMIZED, PHASE II TRIAL OF KETOCONAZOLE PLUS ALENDRONATE VERSUS KETOCONAZOLE ALONE IN PATIENTS WITH ANDROGEN INDEPENDENT PROSTATE CANCER AND BONE METASTASES

WILLIAM D. FIGG,* YINONG LIU, PHILIP ARLEN, JAMES GULLEY, SETH M. STEINBERG, DAVID J. LIEWEHR, MICHAEL C. COX, SUOPING ZHAI, SERGE CREMERS, ALLYSON PARR, XIAOWEI YANG, CLARA C. CHEN, ELIZABETH JONES AND WILLIAM L. DAHUT

From the Center for Cancer Research, National Cancer Institute (WDF, YL, PA, JG, SMS, DJL, MCC, SZ, AP, XY, WLD) and Departments of Nuclear Medicine (CCC) and Diagnostic Radiology (EJ), Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, and Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center (SC), Leiden, The Netherlands

ABSTRACT

Purpose: Alendronate (AL), a potent oral bisphosphonate, blocks the secretion of matrix metalloproteinase-2 and the establishment of bone metastases in animal models. Ketoconazole (KT) has demonstrated activity in androgen independent prostate cancer (AIPC). In this study we determined whether KT plus AL produced acceptable disease responses compared with KT alone. As the experimental design, 72 patients with progressive AIPC metastatic to bone were randomized to receive KT (1,200 mg daily) plus hydrocortisone (H) (30 mg daily) with or without AL (40 mg daily). Prostate specific antigen (PSA) consensus criteria and radiographic scans were used to determine the proportion of patients with a PSA decrease, time to progression and response duration. The pharmacokinetics of KT and AL were characterized and changes in circulating angiogenic factors were assessed.

Results: At a median potential followup of 23.9 months the proportion of patients with a greater than 50% decrease in PSA was similar in the KT/H/AL and KT/H, groups (50% and 47%, respectively). The median duration of response was 8.9 and 6.3 months in the KT/H/AL and KT/H groups, respectively ($p = 0.125$). Median progression-free survival was not significantly prolonged in the KT/H/AL group (4.6 vs 3.8 months, $p = 0.27$). There was no significant difference in overall survival between the 2 treatment arms but there was a trend toward improved survival in the KT/H arm ($p = 0.074$). Toxicity in the 2 groups was mild and there were no clear associations between changes in circulating angiogenic factor levels and clinical outcomes in either treatment arm.

Conclusions: There were no statistically significant differences in response rate, progression-free survival or overall survival between KT/H alone and KT/H plus AL treatment in patients with AIPC. The addition of AL to KT/H may increase the response duration with an acceptable safety profile compared with treatment with KT/H alone. However, the addition of AL offers no survival benefit in patients with AIPC.

KEY WORDS: prostate, prostatic neoplasms, ketoconazole, alendronate, pharmacokinetics

Prostate cancer is currently the second leading cause of cancer related deaths with 28,900 deaths estimated in 2004.[1] Although the majority of patients with advanced prostate cancer respond to hormonal therapy, androgen independence eventually occurs and it is ultimately fatal. Single agent or combination chemotherapy may lead to improved quality of life and survival[2] but not without toxicities. Therefore, new therapeutic modalities for the treatment of prostate cancer are warranted.

Bisphosphonates inhibit osteoclast mediated bone resorption.[3] They may decrease bone pain and skeletal complications in patients with metastatic cancer[4–6] and improve survival in multiple myeloma.[7] The bisphosphonate alendronate (AL) has been shown to inhibit osteoclast activity, block the establishment of bone metastases[8,9] and inhibit the secretion of matrix metalloproteinase (MMP)-2, which in turn may block angiogenesis.

The antimycotic agent ketoconazole (KT) is a potent inhibitor of adrenal steroid synthesis and it is used as second line hormonal treatment in patients with androgen independent prostate cancer (AIPC). The rate of a prostate specific antigen (PSA) decrease of greater than 50% with KT treatment ranges from 30% to 80%.[10,11] We have reported that KT has an antiproliferative effect on prostate cancer cells in vitro,[12] which may be mediated through cytochrome P450 enzymes other than those responsible for steroidogenesis. These observations suggest that there is a direct cytotoxic effect of KT on tumor cells rather than simply an effect of androgen regulation. Based on these data a randomized, phase II trial of KT in combination with AL vs KT alone in patients with AIPC and bone metastases was initiated to assess the clinical efficacy of this combination.

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* Correspondence: National Cancer Institute, 10 Center Dr., Building 10, Room 5A-01, Bethesda, Maryland 20892 (telephone: 301-402-3622; FAX: 301-402-8606; e-mail: wdfigg@helix.nih.gov).

PATIENTS AND METHODS

Protocol objectives. The primary objective was to determine if KT plus AL produced acceptable disease responses compared with KT alone. Other objectives were to characterize the pharmacokinetics and pharmacodynamics of the 2 agents, and determine the extent of angiogenesis inhibition.

Patient eligibility. All patients had AIPC metastatic to bone and had progressed after combined androgen blockade and antiandrogen withdrawal. Each patient had 1) a histological diagnosis of adenocarcinoma of the prostate, 2) increasing PSA despite continued testicular suppression and/or progression on computerized tomography (CT) or bone scan and 3) an Eastern Cooperative Oncology Group performance status of 2 or less. There were no limits on prior radiation or chemotherapy.

Study design. This was an open label, randomized, phase II study of KT (400 mg 3 times daily with 20 mg hydrocortisone every morning and 10 mg hydrocortisone every evening) plus AL (40 mg daily) vs KT with hydrocortisone (H) as described alone in patients with AIPC. The trial was designed to enroll 36 patients per arm to permit the study to conclude whether the response proportion on each arm was 40% or greater as opposed to 20% with 10% types I and II error probabilities. The study used a new method of interim evaluation of responses, which would have permitted the study to terminate early in the event that 1 arm had far superior responses than the other at a midpoint.[13] This study was approved by the institutional review board of the National Cancer Institute and all patients provided informed consent.

Concomitant administration of drugs that decrease gastric acid output or increase gastric pH were prohibited. PSA, standard chemistry and hematological tests were obtained monthly. Radiographic studies (CT of the chest, abdomen and pelvis, and ^{99m}technetium bone scintigraphy) were repeated every 2 months. Therapy continued if there were no significant toxicities or evidence of disease progression. In addition, patients who had not undergone bilateral orchiectomy continued to receive luteinizing hormone-releasing hormone agonist.

The dose of KT was decreased by 200 mg daily and that of AL was decreased by 10 mg daily in patients who experienced Common Toxicity Criteria, version 2.0, grade 2 side effects until they subsided. Patients who experienced grades 3 to 4 toxicity had the drug withheld until toxicity resolved to grade 2 or less. Patients were allowed to resume treatment at a decreased dose within 2 months provided that the side effect had resolved or decreased in severity to grade 2 or less. Patients in whom symptoms did not decrease after a 2-month hiatus off treatment were withdrawn from further study participation.

Response evaluation. Standard objective criteria were used to assess soft tissue lesion changes.[14] Disappearance of greater than 50% of the number of metastatic lesions on bone scan was also considered a positive response. PSA criteria for response and progression were based on Working Group Consensus of PSA criteria.[15] Briefly, PSA response was defined as a decrease in PSA of 50% or greater (confirmed by a second value at 4 weeks or greater after the first one) with no other evidence of disease progression. Progressive disease was defined by any of certain criteria, including 1) a greater than 25% increase in the size of all soft tissue masses and/or the appearance of new masses, 2) the need for radiation therapy and 3) 2 consecutive increasing PSA measurements by 50% or greater of nadir PSA in patients with a PSA response, by 25% or greater of nadir or baseline (whichever was lower) PSA in patients without a PSA response or by new lesions consistent with AIPC. Patients were not declared to have disease progression until PSA had increased by an absolute value of 5 ng/ml or greater.

KT pharmacokinetic analysis. Serial blood samples were collected following a single dose and KT plasma concentrations were determined using high performance liquid chromatography assay.[15] Data were analyzed by noncompartmental and compartmental analysis (ADAPT II, version 4, University of Southern California, Los Angeles, California). A 1 compartment model with absorption delay was applied.

AL pharmacokinetic analysis. Urine concentrations of alendronate were analyzed by high performance liquid chromatography assay with a limit of quantitation of 4 ng/ml.[16]

Assessment of changes in circulating angiogenic growth factors. Plasma was collected for the determination of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) levels prior to study and at each clinic visit thereafter. From each arm of the trial 10 patients with a PSA decrease of 50% or greater and 10 without a PSA decrease serving as controls were assayed for VEGF and bFGF levels using enzyme-linked immunosorbent assay (ELISA) kits (R and D Systems, Minneapolis, Minnesota).[17] Changes in MMP-2 and MMP-9 were also examined. (Amersham Pharmacia Biotech, Piscataway, New Jersey). All analyses were performed in duplicate and the absolute values obtained from each ELISA plate were back calculated from the ELISA kit standard curve.

Assessment of changes in bone resorption. Serum levels of cross-linked N-telopeptides of type I collagen (NTx) were measured using an ELISA assay (Osteomark Serum NTx ELISA kit, Wampole Laboratories, Princeton, New Jersey).[18] Final assay results are reported as nanomoles of bone collagen equivalents (BCE)/l.

Statistical analysis. All patients who received any experi-

TABLE 1. *Demographics of patients enrolled*

	KT/H	KT/H/AL
No. pts	36	36
Median age (range)	70 (51–79)	72 (51–85)
Median Gleason score at diagnosis (range)	8 (3–9)	8 (4–9)
Median ng/ml baseline PSA (range)	74.35 (1.7–1,458)	78.1 (5.5–1,562)
No. soft tissue lesion(s)	10	8
No. prior palliative radiotherapy	6	7
No. secondary hormonal therapies	23	21
No. chemotherapy	8	7
No. opioid analgesics prior to enrolling	7	9
Eastern Cooperative Oncology Group performance status:		
0	12	7
1	23	25
2	1	4
Median U/l lactate dehydrogenase (range)	198.5 (122–397)	196 (137–525)
Median IU/l alkaline phosphatase (range)	130.5 (69–924)	134.5 (71–4,000)
Median gm/dl glucose (range)	116.5 (80–273)	113 (83–255)
Median gm/dl hemoglobin (range)	12.7 (8.7–15.3)	13.05 (9–15.4)
Median 1,000/mm^3 platelets (range)	239.5 (101–401)	223 (132–408)

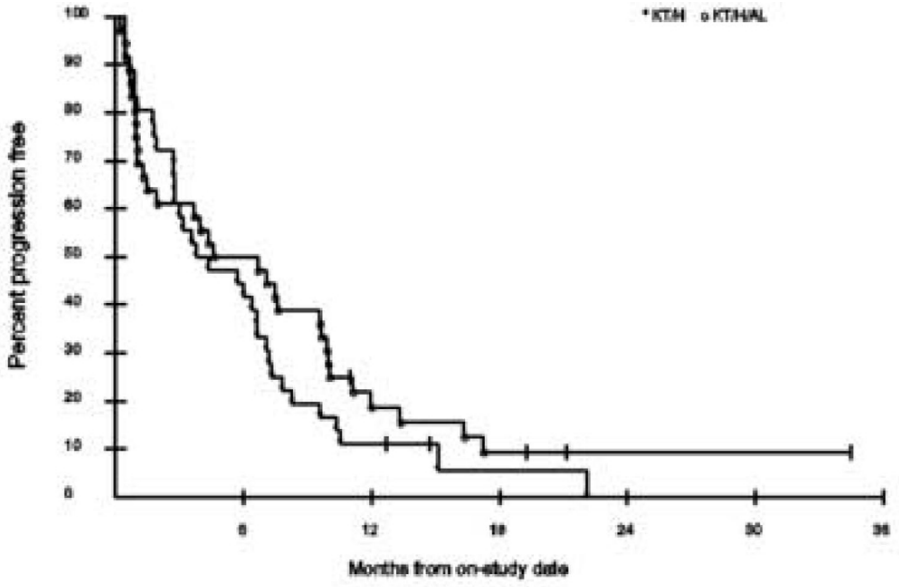

FIG. 1. Kaplan-Meier graph shows PFS in KT/H and KT/H/AL groups (median 3.8 and 4.6 months, respectively)

mental drugs were evaluable for toxicity and disease response. Overall survival and progression-free survival (PFS) duration were calculated from the on-study date until the date of death, progression or last followup, as appropriate. Response duration was calculated from the date of response until the date of progression or last followup. The probability of survival, progression-free survival or continued response was determined by the Kaplan-Meier method. The statistical significance of the difference between a pair of Kaplan-Meier curves was determined by the Mantel-Haenszel method. The statistical significance of the difference between the 2 randomized groups with respect to various laboratory parameters was determined by the Wilcoxon rank sum test. All p values are 2-sided.

RESULTS

Patient data. A total of 72 patients were accrued (36 patients per arm) with a median potential followup of 23.9 months. Table 1 lists demographic data. At study entry patient characteristics were similar in the 2 treatment groups (table 1). The majority of patients received second line hormonal therapy prior to this study and 15 received prior chemotherapy.

Clinical activity. The proportion of patients with a 50% or greater decrease in PSA was similar between the 2 groups, namely 17 of 36 (47%) in the KT/H arm and 18 of 36 (50%) in the combination group. A total of 18 patients had measurable disease on CT. No individual had a partial response by CT criteria, although several patients had some decrease in measurable disease (50% or less decrease). All patients had evaluable disease by bone scan. None of the patients had a normalization of bone scan. There was no significant difference in PFS between the 2 treatment arms (fig. 1). Median PFS in the KT/H and KT/H/AL groups was 3.8 and 4.6 months, respectively ($p = 0.27$). However, there was a trend toward a prolonged response duration by adding AL. Figure 2 shows

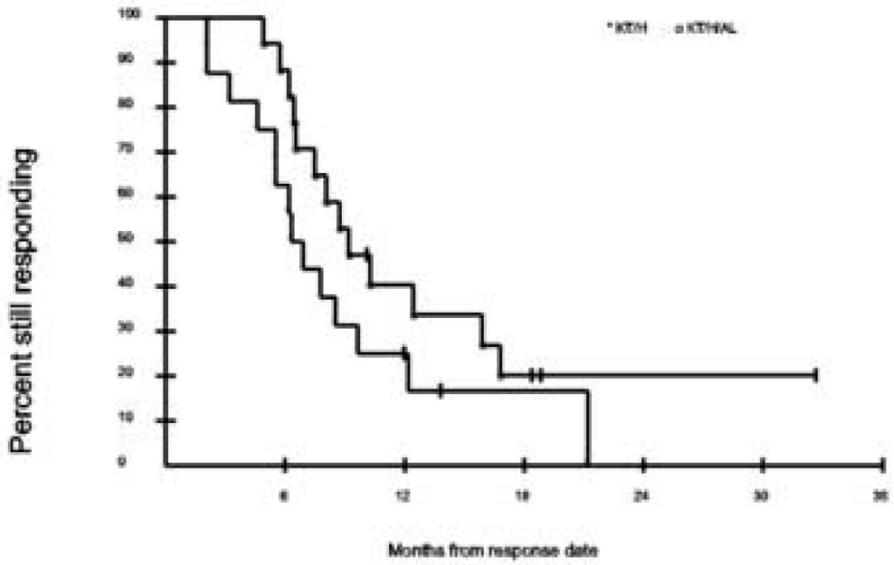

FIG. 2. Kaplan-Meier graph demonstrates response duration in KT/H and KT/H/AL groups (median 6.3 and 8.9 months, respectively)

that the median duration of response was 6.3 months in the KT/H group and 8.9 months in the KT/H/AL group ($p = 0.125$). At the time of analysis 14 of 16 responders in the KT/H group and 13 of 17 in the combined group had progressed. A total of 43 patients are currently alive and the median survival duration was 24.7 months (fig. 3, *A*). There was no statistically significant difference in overall survival between the 2 treatment arms. However, median overall survival in KT/H/AL group was 19.0 months and it has not been achieved in the KT/H group ($p = 0.074$, fig. 3, *B*).

Toxicity. All patients who received any treatment were evaluated for toxic effects. Overall toxicities were mild and there was no significant difference between the 2 arms (table 2). Of the patients 28 (39%) had grades 1 and 2 nausea and/or emesis, and 40 (56%) had fatigue, including 3 with grade 3 symptoms. Seven patients (10%) had grade 1 or 2 and 1 had grade 3 reversible liver function test abnormalities. Grade 1 skin toxicity, including dryness, dry lips, mild loss of body hair and skin stickiness (19 patients) was observed in 69% of patients. Eight patients experienced grade 3 toxicities. The incidence of grade 3 toxicity was only slightly higher for KT/H/AL (5 patients) compared with the KT/H arm (3 patients). One patient in the combination arm had a duodenal ulcer with upper gastrointestinal bleeding. There were no grade 4 or 5 events. A total of 11 patients (15%) had hyperglycemia at least once during therapy but only 2 required treatment. Three patients experienced a mild increase in creatinine, which returned to normal after conservative managements.

Pharmacokinetics. Pharmacokinetic analysis was performed in 21 patients who received a single initial dose of 400 mg KT on day 1. Figure 4 shows the plasma concentration-time profile. Ten hours after administration KT concentrations were usually low or below the limit of quantitation (62.5 ng/ml). A 1 compartment model with absorption delay fit the data well ($r^2 = 0.97$). The elimination half-life was 1.9 hours

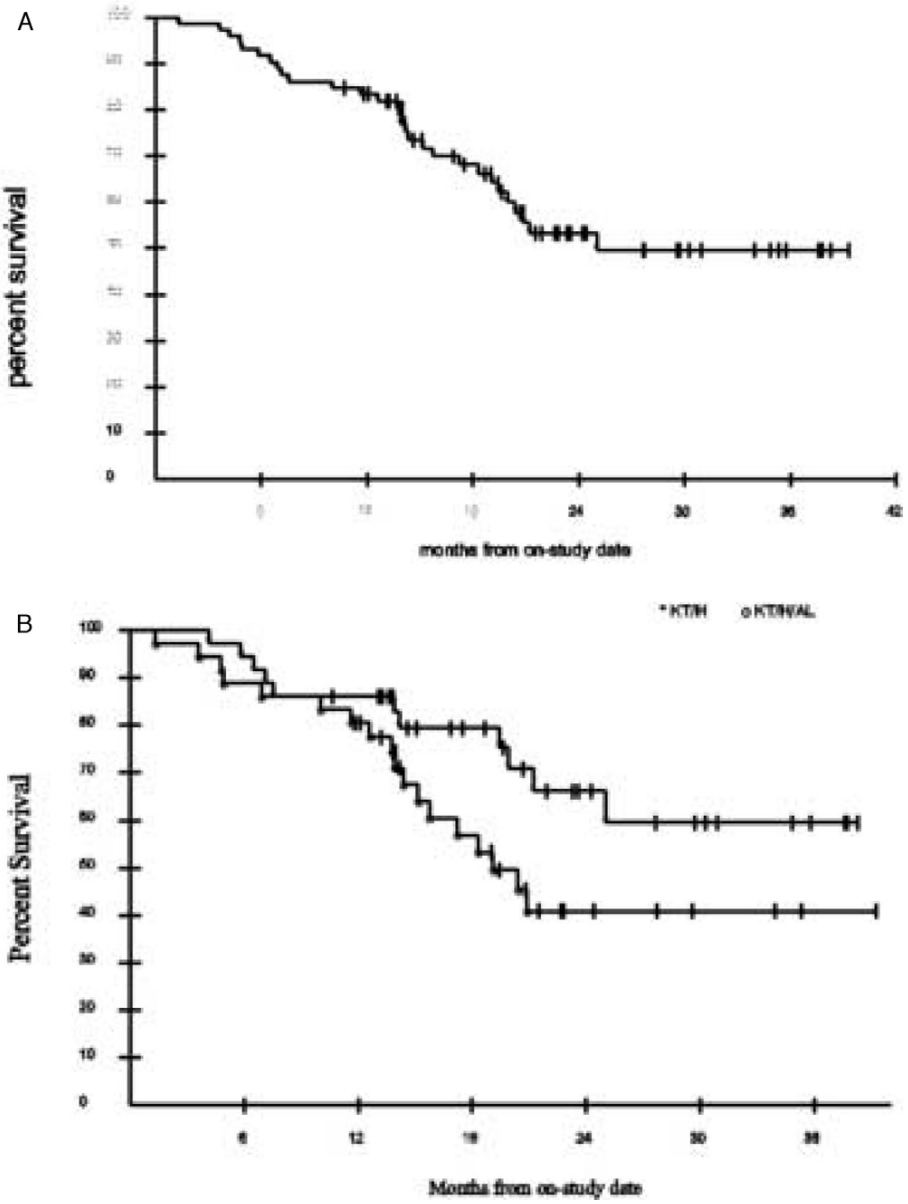

FIG. 3. Kaplan-Meier graph shows overall survival. *A*, in all patients median survival was 24.7 months. *B*, in KT/H and KT/H/AL groups median survival was 19 months and not achieved, respectively.

TABLE 2. *Most frequent treatment related adverse events*

	No. KT/H/AL (%)		No. KT/H (%)	
	Grades 1–2	Grade 3	Grades 1–2	Grade 3
No. pts	36		36	
Whole body:				
Fatigue	16 (44)	2 (6)	21 (58)	1 (3)
Edema	10 (28)		5 (14)	
Hot flash	2 (6)		5 (14)	
Headache	6 (17)		3 (8)	
Tearing	2 (6)		4 (11)	
Digestive system:				
Nausea/vomiting	12 (33)		16 (44)	
Dyspepsia	9 (25)		5 (14)	
Diarrhea	9 (25)		7 (19)	
Constipation	9 (25)		7 (19)	
Taste disturbance	3 (8)		8 (22)	
Duodenal ulcer with gastrointestinal bleeding		1 (3)		
Nervous system:				
Dizziness	7 (19)		2 (6)	
Blurred vision	2 (6)		3 (8)	
Skin:				
Dry skin/lips	24 (67)		26 (72)	
Rash	3 (8)		5 (14)	
Metabolic + other laboratory abnormalities:				
Hyperglycemia	4 (11)	2 (6)	4 (11)	1 (3)
Increased serum glutamic-pyruvic transaminase	3 (8)		3 (8)	1 (3)
Increased serum glutamic-oxaloacetic transaminase	4 (11)		3 (8)	1 (3)
Increased creatinine	2 (6)		1 (3)	

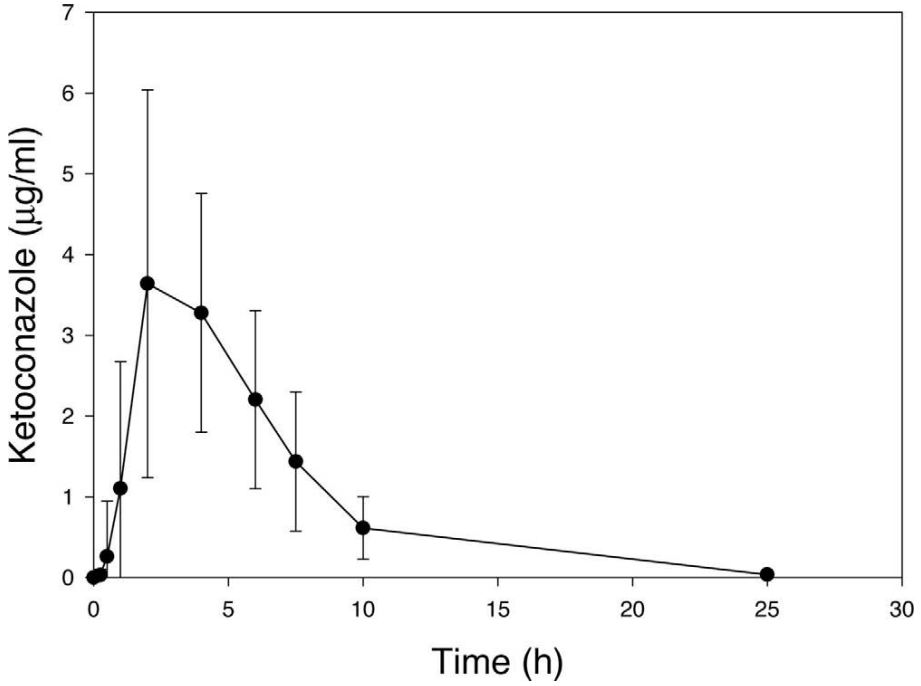

FIG. 4. Mean KT plasma concentration-time profile data ± SD on 21 patients

(table 3). KT clearance was 22.6 l per hour, similar to that obtained with compartmental analysis (22.0 l per hour). The mean concentration at steady state ± SD of KT alone and KT plus AL was 6.0 ± 3.0 and 6.5 ± 3.7 µg/ml, respectively. There was no significant difference between the 2 groups (unpaired *t* test $p > 0.05$). Of 36 patients who received AL 34 achieved a steady-state urine concentration. Patients had a mean urine concentration of 488 ng/ml (range 8 to 2,555), which was within that anticipated for this dose.

Changes in bone resorption. A total of 66 patients were evaluable for changes in NTx. There were 34 patients in the K alone group with a mean decrease of 3.39 nM BCE/l (range −74.9 to 75.1) and 32 in the KT/AL group with a mean decrease of 25.97 nM BCE/l (range −52.1 to 571.7). Overall there was a mean decrease of 29.37 ± 73.78 nM BCE/l and the difference was not statistically significant between the 2 groups ($p = 0.11$).

Changes in the levels of circulating angiogenic growth factor. We analyzed VEGF, bFGF, MMP-2 and MMP-9 levels at baseline and during treatment as potential indicators of the biological activity of alendronate. Plasma circulating VEGF and bFGF levels were evaluated in 10 patients with a PSA response and in 10 without a response per group. The relationship between changes in PSA (classified as a PSA re-

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