Increases in bone turnover marker levels at an early phase after starting zoledronic acid predicts skeletal-related events in patients with prostate cancer with bone metastasis

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Increases in bone turnover marker levels at an early phase after starting zoledronic acid predicts skeletal-related events in bone metastatic prostate cancer patients

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Abstract

Objective:

- To examine whether bone turnover markers could be predictive markers of the probability of newly arising SRE after the start of zoledronic acid treatment in prostate cancer patients with bone metastasis.

Patients and Methods:

- Thirty prostate cancer patients with bone metastasis were treated with zoledronic acid infusion every 4 weeks.
- Serum C-terminal crosslinking telopeptide of type 1 collagen (1CTP), bone alkaline phosphatase (BAP), and prostate-specific antigen (PSA) were measured at the start of zoledronic acid treatment to establish baseline values, and every 4 weeks thereafter.
- To judge in the early phase whether zoledronic acid is effective in these patients, we retrospectively compared 1CTP, BAP, and PSA levels at 1, 3, and 6 months after starting zoledronic acid treatment with those at baseline.

Results:

- SRE-free survival (SFS) of patients with increases of 1CTP at 1 and 3 months and

BAP at 3 months were significantly poorer than those of patients with decreases in 1CTP or BAP (P = 0.001, P = 0.042, and P = 0.004, respectively).

- Overall survival (OS) of patients with increases of 1CTP at 1 and 3 months and of BAP at 6 months were significantly poorer than those of patients with decreases of 1CTP or BAP (P = 0.013, P = 0.027, and P = 0.035, respectively).

Conclusion:

- The measurement of 1CTP and BAP at an early phase after starting zoledronic acid treatment may be useful for physicians to inform patients of their prognosis and to determine the subsequent treatment plan.

Key words: bone metastasis, bone turnover marker, prostate cancer, zoledronic acid, skeletal-related events

Introduction

Prostate cancer (PCa) is the most frequent malignancy in men. In Europe, about 382,000 men (11.9% of all cancers) were diagnosed with prostate cancer in 2008 [1]. In the USA, about 192,280 men (25.1% of male cancers) were diagnosed with prostate cancer in 2009, and this disease is the second most frequent cause of cancer-related death in men [2]. Although hormone therapy is useful for advanced PCa, its effects are limited and PCa cells become castration-resistant PCa (CRPC) after several years [3,4]. Skeletal metastasis occurs in approximately 80% of patients with advanced PCa, and no curative therapies are available for bone metastatic CRPC [5,6]. Complications from bone metastases are a major cause of morbidity in patients with PCa, causing pain, spinal cord compression, pathological fractures, and abnormalities in serum calcium levels [7]. Although zoledronic acid at 4 mg reduced skeletal-related events (SRE) in PCa patients with bone metastases [8], it is not effective for all patients with PCa and the duration of the effect is unclear. It was reported that serum bone alkaline phosphatase (BAP) and C-terminal crosslinking telopeptide of type 1 collagen (1CTP) in patients with metastatic bone progression were significantly higher at months 6, 9, 12, and 15 after starting treatment with zoledronic acid compared to those without

progression [9]. Although bone turnover markers provide valuable information regarding progression of bone metastasis in men with metastatic PCa under zoledronic acid treatment, there are no evident biomarkers predicting SRE or survival after starting zoledronic acid treatment. In the present study, we examined whether the early changes in serum 1CTP, BAP, and prostate-specific antigen (PSA) levels could be predictive markers of the probability of newly arising SRE.

Patients and Methods

Patients

Between June 2006 and March 2010, Japanese PCa patients with bone metastasis treated with zoledronic acid (Zometa; Novartis Pharma, Nurnberg, Germany) at Kanazawa University Hospital were analyzed. All patients were histologically diagnosed as PCa. 1CTP, BAP, and PSA of PCa patients with bone metastasis treated with zoledronic acid were measured at the start of treatment to obtain baseline values, and every 4 weeks thereafter. Zoledronic acid infusion at 4 mg was also performed every 4 weeks. All antineoplastic therapies for PCa after starting zoledronic acid were permitted. This retrospective analysis was performed in accordance with the Declaration of Helsinki.

Methods

The variables analyzed were patient age, PSA, extent of disease on bone scan (EOD) [10] at diagnosis and at the start of zoledronic acid treatment, and 1CTP, BAP, and condition of PCa (CRPC or not CRPC) at the start of zoledronic acid treatment, prior history of SRE, and Gleason score. Continuous variables were made discrete using

median values as a cutpoint. 1CTP, BAP, and PSA levels at 1, 3, and 6 months after starting zoledronic acid treatment were compared with those at baseline. SRE were defined as pathological bone fractures, spinal cord compression, surgery to bone, radiation therapy to bone, or a change in antineoplastic therapy to treat bone pain [8]. The date of starting zoledronic acid treatment was used as the start of the observation period. SRE-free survival (SFS) was defined as the duration from the start of observation to the date of the first SRE after starting zoledronic acid treatment. Overall survival (OS) was defined as the duration from the start of observation to the date of death. We analyzed differences between SFS and OS of patients with decreases and with increases in biomarkers at each landmark time compared with baseline.

Statistical analysis

Statistical analyses were performed using commercially available software (PRISM and SPSS, version 17.0). SFS was the study endpoint and OS was also analyzed in this setting. The crude probabilities of newly arising SRE and survival were estimated using the Kaplan-Meier method. Univariate analysis of differences between patient groups was performed with the log rank test. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

Patient characteristics are shown in Table 1. A total of 30 patients were included in this analysis. Median 1CTP, BAP, and PSA at the start of zoledronic acid treatment were 5.2 ng/mL (normal range: < 4.5 ng/mL), 46.7 U/L (normal range: 13.0 – 33.9 U/L), and 200 ng/mL (normal range: < 4.0 ng/mL), respectively. Six patients had a past history of SRE. Before starting zoledronate treatment, changes in antineoplastic therapy to treat bone pain, spinal cord compression, and radiation therapy to bone were reported in 3, 2, and 1 patients, respectively.

Changes of biomarkers at each landmark time compared with baseline

Median 1CTP, BAP, and PSA decreased with time after starting zoledronic acid treatment. Although the number of patients with a decrease in 1CTP compared with baseline decreased gradually, the number of patients with a decrease of BAP compared with baseline increased with time after starting zoledronic acid treatment. Follow-up durations of 2 patients were not reached at 6 months (Table 2).

SFS and OS

After starting zoledronic acid treatment, SRE occurred in 9 patients; change in antineoplastic therapy to treat bone pain (n = 4), radiation therapy to bone (n = 4), and surgery to bone (n = 1). The results of Kaplan–Meier analyses of SFS are shown in Fig. 1. SFS of patients with decreases in 1CTP at 1 and 3 months compared with baseline were significantly better than those of patients with increases in 1CTP (P=0.001 and P=0.042, respectively). SFS of patients with a decrease in BAP at 3 months compared with baseline was significantly better than that of patients with an increase in BAP (P = 0.004). There were no differences between SFS of patients with decreases and with increases of PSA at any landmark time compared with baseline. Three patients died after starting zoledronic acid treatment, and the cause of death was PCa in all cases. The results of Kaplan–Meier analyses of OS are shown in Fig. 2. OS of patients with decreases in 1CTP at 1 and 3 months compared with baseline were significantly better than those of patients with increases in 1CTP (P = 0.013 and P = 0.027, respectively). OS of patients with a decrease in BAP at 6 months compared with baseline was significantly better than that of patients with an increase in BAP (P = 0.035). There were no differences between OS of patients with decreases and with increases in PSA compared with baseline at any landmark time. The results of univariate analyses of

variables and SFS, and OS are shown in Table 3. There were no significant differences between the two categorized groups of each variable.

Adverse events

Osteonecrosis of the jaw was observed in 4 patients. Zoledronic acid was withdrawn permanently in 2 patients and temporarily in 2 patients (for 3 and 4 months, respectively). The remaining 26 patients had no major adverse events and zoledronic acid treatment was continued up to the last follow-up date.

Discussion

Since a large international randomized placebo-controlled trial on the treatment of metastatic bone disease of PCa with zoledronic acid has been reported [8], zoledronic acid has become a standard supportive therapy for PCa with bone metastasis. The trial showed a 41% reduction in risk of skeletal morbidity, a sustained beneficial effect on bone pain, and reductions in bone marker levels among patients receiving zoledronic acid. However, the percentage of patients without SRE at 15 months with zoledronic acid treatment at 4 mg was 55.1% [8]. Urological practitioners and medical oncologists are eager to predict the effects of zoledronic acid treatment in individual patients. Therefore, several studies have been performed to predict SRE or cancer-specific death using a variety of bone turnover markers, because the measurement of bone turnover markers has become more common in recent trials in patients with bone metastases. Assessment of these markers provides specific insight into rates of bone formation and resorption, and levels seem to be correlated with bone pain levels and the burden of disease in the skeleton [11-14]. Lein *et al*. reported that cross-linked N-terminal (NTx) and cross-linked C-terminal (CTx) telopeptides of type 1 collagen, and amino-terminal procollagen propeptides of type 1 collagen (P1NP) in PCa patients with metastatic bone

progression were significantly higher after starting treatment with zoledronic acid compared to those without progression [9]. Lipton *et al*. reported that normalized NTx within 3 months of treatment, versus persistently elevated NTx, after starting zoledronic acid was associated with reduced risks of skeletal complications and death in patients with bone metastasis from solid tumors including PCa [15]. On the other hand, Mountzios *et al*. measured bone turnover markers including the receptor activator of nuclear factor kappa-B ligand, osteoprotegerin, CTx, tartrate-resistant acid phosphatase isoform 5b, and osteopontin at the onset of skeletal metastases and after 6 months of treatment with zoledronic acid in 70 patients and concluded that none of the markers was able to predict skeletal morbidity or clinical outcomes independently. However, their study included only 22 PCa patients (31%) and assessments of bone turnover markers were not performed at an early phase after starting zoledronic acid [16]. 1CTP and BAP were also used as markers of bone resorption and bone formation, respectively. Brown *et al*. reported that baseline and on-study bone turnover marker levels were predictive of negative clinical outcomes in patients with bone metastases secondary to PCa and to non-small cell lung cancer and other solid tumors [17]. In their study, levels of serum BAP were assessed every 3 months for patients with bone metastasis and were categorized as low or high. In the PCa group, compared with patients who had low

baseline BAP levels, those with high BAP levels had a significantly increased risk of experiencing SRE (relative risk = 1.85, *P* = 0.012) or of dying (relative risk = 1.83, *P* = 0.006). In addition, patients with high on-study BAP levels had a significant 1.6-fold increase in the risk of disease progression compared with patients who had low on-study BAP levels (relative risk = 1.64, *P* = 0.018). They subsequently reported that significant baseline prognostic factors for occurrence of first SRE in breast cancer patients by multivariate analyses included age, pain score, prior history of SRE, predominant lesion type, and elevated BAP and lactate dehydrogenase levels [18]. On the other hand, Lein *et al*. reported that the percentage change of 1CTP was the most indicative for SRE during treatment with zoledronic acid [19]. They also reported that in patients with metastatic bone progression 1CTP and BAP were significantly higher at months 6, 9, 12, and 15 after starting treatment with zoledronic acid compared to patients without progression [9]. However, bone turnover marker levels at an early phase after starting zoledronic acid treatment were hardly examined with regard to SFS and OS. Moreover, there have been no reports comparing on-study bone turnover marker levels after starting zoledronic acid treatment with baseline levels in analyzing SFS and OS. In the present study, none of the baseline variables, including 1CTP, BAP, and PSA at the start of zoledronic acid, were significant predictors of SFS and OS. Nevertheless, SFS and

OS of patients with increases in 1CTP at 1 and 3 months after starting zoledronic acid treatment compared with baseline were significantly poorer than those of patients with decreases in 1CTP. There were no significant differences between SFS and OS of patients with increases in BAP at 1 month after starting zoledronic acid treatment compared with baseline and those of patients with a decrease in BAP. However, SFS of patients with an increase in BAP at 3 months after starting zoledronic acid treatment compared with baseline were significantly poorer than those of patients with a decrease in BAP. OS of patients with an increase in BAP at 6 months after starting zoledronic acid treatment compared with baseline was also significantly poorer than that of patients with a decrease in BAP. These results were consistent with the mechanisms of zoledronic acid and the theory of bone metastasis [20]. Presumably, because zoledronic acid initially inhibits osteoclasts, subsequent inactivation of osteoblasts is induced; a decrease in BAP was observed after a decrease in 1CTP level in patients in whom zoledronic acid was effective. On the other hand, zoledronic acid may not have strong antineoplastic ability because PSA changes following zoledronic acid treatment did not predict SFS or OS in the present study. This suggests that even if PSA increases just after starting zoledronic acid treatment, this treatment should not be withdrawn.

Our study had a number of limitations. The small sample size may have prevented

determination of the precise statistical significance of differences between groups. Larger prospective studies with longer follow-up periods and data from other ethnic backgrounds are needed to confirm our findings. The changes of other bone turnover markers, such as NTx or PINP, at an early phase after starting zoledronic acid may also predict SFS or OS. Therefore further study should include more markers. Moreover, because a variety of antineoplastic treatments, including docetaxel, alternative antiandrogens, estramustine phosphate, and dexamethasone for CRPC, were performed [21-25], some factors, especially PSA, SFS, and OS may not have been impacted only by zoledronic acid.

Finally, the present study indicated that although 1CTP, BAP, and PSA at baseline were not predictors of SFS and OS, increases in 1CTP at 1 and 3 months and in BAP at 3 months after starting zoledronic acid treatment compared with baseline were negative predictive factors for SFS, and the increases in 1CTP at 1 and 3 months and in BAP at 6 months after starting zoledronic acid treatment compared with baseline were negative predictive factors for OS. To our knowledge, this is the first report to clarify that the changes in 1CTP and BAP at an early phase after commencement of zoledronic acid treatment predict SFS and OS in PCa patients with bone metastasis.

Conclusions

The measurement of 1CTP and BAP at an early phase after starting zoledronic acid treatment may be useful for physicians to inform patients of their prognosis and to determine the subsequent treatment plan.

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Figure legends

Fig. 1 The results of Kaplan–Meier analyses of SFS are shown. SFS of patients with decreases in 1CTP at 1 and 3 months compared with baseline were significantly better than those of patients with increases in 1CTP ($P = 0.001$ and $P = 0.042$, respectively). SFS of patients with a decrease in BAP at 3 months compared with baseline was significantly better than that of patients with an increase in BAP ($P = 0.004$). Solid lines indicate patients with decreases in biomarkers compared with baseline. Dotted lines indicate patients with an increases in biomarkers compared with baseline.

Fig. 2 The results of Kaplan–Meier analyses of OS are shown. OS of patients with decreases in 1CTP at 1 and 3 months compared with baseline were significantly better than those of patients with increases in 1CTP ($P = 0.013$ and $P = 0.027$, respectively). OS of patients with a decrease in BAP at 6 months compared with baseline was significantly better than that of patients with an increase in BAP ($P = 0.035$). Solid lines indicate patients with decreases in biomarker levels compared with baseline. Dotted lines indicate patients with increases in biomarkers compared with baseline.

Table 1. Patient characteristics

Patients, n		30
Median age at diagnosis		65.5 (46 – 83)
Median PSA ng/mL at diagnosis		200 (6 – 4370)
Median age at start of zoledronic acid treatment		71 (46 – 84)
Median 1CTP ng/mL at start of zoledronic acid treatment		5.2 (2.3 – 73)
Median BAP U/L at start of zoledronic acid treatment		46.7 (15.5 – 1220)
Median PSA ng/mL at start of zoledronic acid treatment		67.4 (1.6 – 4182)
Median follow-up, months		17 (4 – 49)
Gleason score (%):	7	7 (23)
	8	4 (13)
	9	12 (40)
	10	2 (7)
	Unknown	5 (17)
EOD at diagnosis (%):	0	13 (43)
	1	4 (13)
	2	8 (27)
	3	4 (13)
	4	1 (3)
EOD at start of zoledronic acid treatment (%):	1	9 (30)
	2	6 (20)
	3	13 (43)
	4	2 (7)
Starting zoledronic acid at diagnosis (%):	Yes	6 (20)
	No	24 (80)
CRPC (%):	Yes	20 (67)
	No	10 (33)
Prior SRE (%):	Yes	6 (20)
	No	24 (80)

PSA = prostate-specific antigen; 1CTP = C-terminal crosslinking telopeptide of type 1 collagen; BAP = Bone alkaline phosphatase; EOD = Extent of disease on bone scan; CRPC = Castration-resistant prostate cancer; SRE = Skeletal-related events; Data in parentheses are ranges.

Table 2. Median values and the number of cases of which markers changed compared with baseline

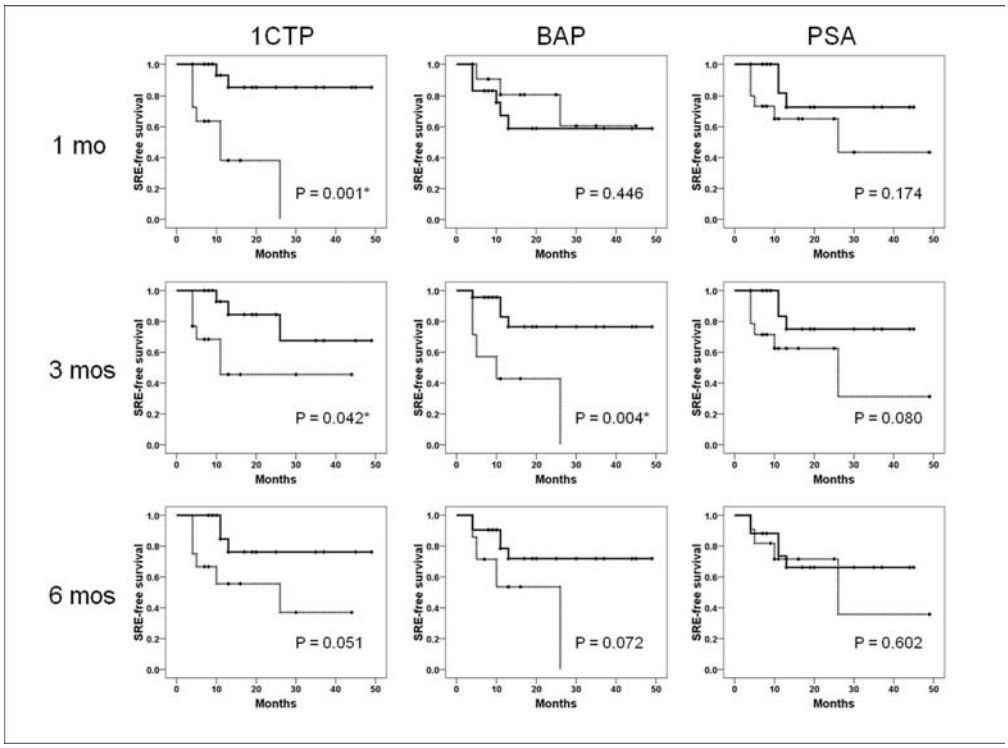
	1CTP			BAP			PSA		
	Median ng/mL	Dec	Inc	Median U/L	Dec	Inc	Median ng/mL	Dec	Inc
At 1 month	4.75 (2.1 – 161)	19	11	39.1 (8.4 – 785)	18	12	27 (0.6 – 1893)	15	15
At 3 months	4.75 (2.1 – 102)	17	13	24.8 (9.3 – 456)	23	7	24.6 (0.6 – 2606)	16	14
At 6 months*	4.65 (2.9 – 94)	16	12	18.8 (8 – 672)	21	7	20.9 (0.2 – 3728)	17	11

Abbreviations as in Table 1. Dec = Decrease; Inc = Increase; Data in parentheses are ranges. *Follow-up of 2 patients were not reached.

Table 3. Univariate analysis of variables and skeletal-related events-free survival and overall survival

Variables	SFS		OS
	HR (95%CI)	p value	HR (95%CI)
Age at diagnosis, 65.5 or older vs. younger	0.833 (0.220 – 3.158)	0.788	0.460 (0.048 – 4.
Age at start of zoledronic acid treatment, 71 or older vs. younger	1.903 (0.481 – 7.521)	0.360	0.599 (0.062 – 5.
PSA ng/mL at diagnosis, 200 or higher vs. lower	0.472 (0.114 – 1.950)	0.300	0.300 (0.029 – 3.
1CTP ng/mL at start of zoledronic acid treatment, 5.2 or higher vs. lo	0.702 (0.184 – 2.671)	0.604	0.412 (0.042 – 4.
BAP U/L at start of zoledronic acid treatment, 47 or higher vs. lower	2.380 (0.619 – 9.150)	0.207	6.391 (0.660 – 6
PSA ng/mLat start of zoledronic acid treatment, 67.4 or higher vs. lo	0.594 (0.153 – 2.307)	0.452	6.085 (0.621 – 5
Gleason score, 9 or 10 vs. 7 or 8	0.877 (0.187 – 4.117)	0.868	6.450 (0.666 – 6
EOD at diagnosis, 1 – 4 vs. 0	1.353 (0.346 – 5.292)	0.664	4.624 (0.423 – 5
EOD at start of zoledronic acid treatment, 3 or 4 vs. 1 or 2	3.956 (0.960 – 16.31)	0.057	2.703 (0.273 – 2
Starting zoledronic acid at diagnosis, yes vs. no	1.181 (0.250 – 5.575)	0.834	1.684 (0.118 – 2
CRPC, yes vs. no	1.347 (0.341 – 5.318)	0.671	1.516 (0.154 – 1
Prior SRE, yes vs. no	2.079 (0.410 – 10.56)	0.377	0.274 (0.018 – 4.

Abbreviations as in Table 1. SFS = SRE-free survival; OS = Overall survival



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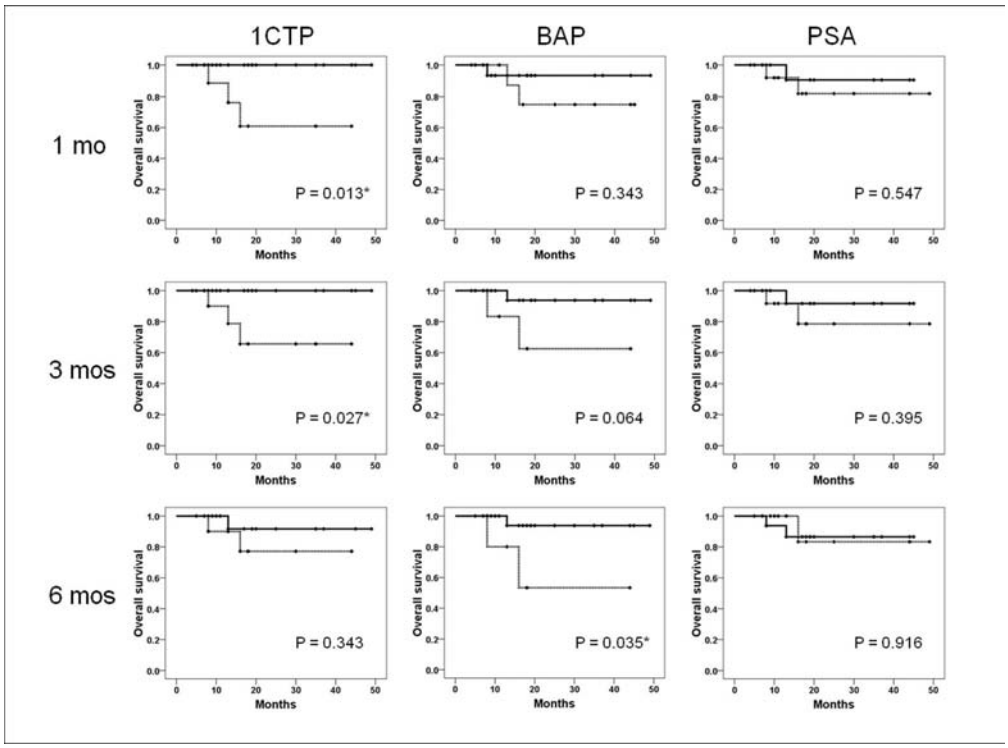

Fig. 2 The results of Kaplan–Meier analyses of OS are shown. OS of patients with decreases in 1CTP at 1 and 3 months compared with baseline were significantly better than those of patients with increases in 1CTP (P = 0.013 and P = 0.027, respectively). OS of patients with a decrease in BAP at 6 months compared with baseline was significantly better than that of patients with an increase in BAP (P = 0.035). Solid lines indicate patients with decreases in biomarker levels compared with baseline. Dotted lines indicate patients with increases in biomarkers compared with baseline.
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