Title: Efficacy of bevacizumab-containing chemotherapy for nonsquamous non-small cell lung cancer with bone metastases

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Abstract

Purpose: Skeletal-related events (SREs) negatively affect the quality of life of patients with cancer. Vascular endothelial growth factor receptor (VEGFR)-targeted therapy is effective against bone metastasis in animal models, but the clinical efficacy of anti-VEGFR inhibitors against bone metastases remains unclear. Therefore, we aimed to investigate the efficacy of chemotherapy with bevacizumab, an anti-VEGF antibody, against bone metastases.

Methods: We retrospectively reviewed consecutive patients with nonsquamous non-small cell lung cancer who received first-line platinum-based chemotherapy with zoledronic acid at Shizuoka Cancer Center between 2007 and 2011.

Results: Of 25 patients, 13 received bevacizumab-based chemotherapy (BEV group), and 12 received chemotherapy without bevacizumab (non-BEV group). The overall response (54% vs. 8%, $p = 0.01$) and disease control (100% vs. 50%, $p = 0.01$) rates were higher in the BEV group than in the non-BEV group. The bone-specific response (23% vs. 0%, $p = 0.038$) and disease control (100% vs. 67%, $p = 0.01$) rates were also higher in the BEV group. The median time to progression (TTP) for bone metastases was higher in the BEV group (13.7 months vs. 4.3 months, $p = 0.06$), whereas that for overall disease was similar between the groups (5.7 months vs. 2.6 months, $p = 0.17$). The proportions of patients with SREs were 23% and 50% in the BEV and non-BEV groups, respectively ($p = 0.16$).

Conclusion: Bevacizumab might potentiate the antitumor activity of chemotherapy against systemic disease and bone metastases, prolonging bone-specific TTP and reducing the incidence of SRE.

Key words: bone metastases, skeletal-related event, bevacizumab, chemotherapy

Introduction

The incidence of bone metastases in patients with lung cancer is approximately 30–40%, and the median survival time of patients with such metastases is 7 months [1]. A more recent retrospective review of 435 patients with non-small cell lung cancer (NSCLC) indicated an incidence of 24% for skeletal metastases. In this review, most instances of skeletal metastases (66%) were detected at the time of initial staging [2].

Patients with metastatic bone disease frequently experience osteoclast-mediated bone destruction, resulting in clinically important complications such as a fracture, the need for bone radiation or surgical therapy, spinal cord compression, or hypercalcemia [3-4]. These complications, collectively known as skeletal-related events (SREs) [5-7], lead to pain and decreased quality of life [8]. Thus, SREs have a negative impact on the quality of life, performance status, and functioning of patients with cancer. In a Japanese retrospective review of 259 patients with NSCLC [9], 30% of patients were found to have skeletal metastases during their clinical course, and 50% of these patients had SREs. Among 135 stage IV patients, 41% had skeletal metastases at the initial staging, and 45% had SREs.

Zoledronic acid has been used in patients with bone metastases because the drug can reduce the incidence of SREs and delay time to the first SRE [10]. Recently, the noninferiority of denosumab to zoledronic acid in delaying the time to the first SRE was demonstrated [11]. However, we believe that the efficacy of these drugs cannot be insufficient. The efficacy of chemotherapy against bone lesions in

patients with lung cancer has not been reported previously.

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent, provides a clinical benefit when combined with platinum-based chemotherapy in first-line therapy against advanced nonsquamous (non-Sq) NSCLC [12-14]. In particular, the response rate and progression-free survival (PFS) compared with those of non-bevacizumab–containing chemotherapy are improved by the addition of bevacizumab. Antitumor activity may be induced by the effects of bevacizumab on tumor vasculature, interstitial pressure, and blood vessel permeability, resulting in enhanced delivery of chemotherapy agents to tumor cells [15]. Nagengast et al. demonstrated that bevacizumab distribution to the bone was similar as that to other organs in an ex vivo biodistribution model [16]. Bäuerle et al. reported that bevacizumab significantly inhibited osteolysis, surrounding soft tissue tumor growth, and angiogenesis in an experimental model of breast cancer bone metastasis as visualized on volumetric computed tomography (CT) and magnetic resonance imaging (MRI) [17]. Furthermore, the blocking of VEGF-VEGF receptor (VEGFR)-2 signaling inhibited bone metastasis in animal models of lung cancer [18]. Therefore, VEGF was suggested as a therapeutic target for bone metastasis [19]. Thus, we hypothesized that bevacizumab-containing chemotherapy could have some clinical benefit in patients with non-Sq NSCLC and bone metastases. We retrospectively investigated the efficacy of bevacizumab-containing chemotherapy and compared it to that of chemotherapy without bevacizumab in this study.

Patients and methods

Patients

We reviewed electronic medical records of consecutive patients who visited the Shizuoka Cancer Center between January 2007 and December 2011. In addition, electronically stored images were evaluated by a diagnostic radiologist. Eligible patients were pathologically diagnosed with non-Sq NSCLC, received platinum-based first-line chemotherapy, had bone metastases at the time of receiving chemotherapy, had at least 1 evaluable bone lesion according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [20], and received zoledronic acid continuously. We permitted the inclusion of patients who received EGFR-tyrosine kinase inhibitors before platinum-based chemotherapy. We selected carboplatin plus paclitaxel and carboplatin plus pemetrexed as the non-bevacizumab–containing chemotherapy regimens because we used only these regimens in combination with bevacizumab in our institution. The patients who received bevacizumab-containing chemotherapy comprised the ‘‘BEV group” and those who received chemotherapy without bevacizumab comprised the ‘‘non-BEV group.”

Evaluation

We evaluated the objective response rate, disease control rate, time to progression of overall disease (TTP), time to progression of bone metastases (B-TTP), overall survival (OS), and proportion of patients with SREs. The response to chemotherapy was accessed according to RECIST criteria (version 1.1). At the initial staging, we performed chest and abdominal CT, brain MRI, and positron emission tomography (PET)-CT/bone scintigraphy. To ascertain disease progression or the relapse of overall disease and bone metastases, patients were evaluated by physical examination, chest radiography, and CT of the chest and abdomen. If bone metastases were detected at the initial staging, the patient was regularly followed-up with radiography and CT. If progression of bone metastases was suspected, we additionally performed PET-CT, MRI, or bone scintigraphy, as required. Generally, all patients were evaluated for lesions during and approximately 6–8 weeks after the treatment period.

TTP was measured from the start of first-line chemotherapy to the date of an event of documented disease progression/recurrence or the last follow-up visit. B-TTP was measured from the start of first-line chemotherapy to the date of an event of documented progression of bone metastases and/or SRE or the last follow-up visit. Cases of TTP or B-TTP were censored under the following conditions: no progression or recurrence of overall disease or bone metastases and death. The incidence of SREs accounted for all events that occurred from the start of platinum-based chemotherapy to the date of first progression of overall disease or the last follow-up visit. SREs included a pathologic fracture,

spinal cord compression, and the need for bone radiation or surgical therapy. OS was measured from the start of first-line chemotherapy to the date of death or the last follow-up visit.

Statistical analysis

All categorical variables, objective response rates, and incidences of SREs were analyzed and compared between the BEV and non-BEV groups using the χ^2 test or Fisher's exact test, as appropriate. The distributions of TTP, B-TTP, and OS were estimated using the Kaplan-Meier method, and the BEV and non-BEV groups were compared using the log-rank test. All *p* values were 2-sided, and values less than 0.05 were considered statistically significant. All analyses were performed using JMP 9 software (SAS Institute, Cary, NC). This study was approved by the institutional review board of Shizuoka Cancer Center.

Results

A total of 25 patients, 13 patients in the BEV group and 12 patients in the non-BEV group, were eligible for this retrospective study. Patient characteristics are shown in Table 1. In the BEV and non-BEV groups, the median ages of patients were 63 and 67 years, respectively. In total, 11 of 13 (85%) patients in the BEV group and 9 of 12 (75%) patients in the non-BEV group were men. The BEV group included 11 (85%) current or ever smokers, and the non-BEV group included 7 (58%) current or ever smokers. The numbers of patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 were 12 in the BEV group and 11 in the non-BEV group, and 1 patient in each group had an ECOG PS of 2. The EGFR status was not examined in 5 patients in the non-BEV group, but no statistically significant difference in EGFR status was found between the 2 groups ($p = 0.41$).

The administered chemotherapy regimens are shown in Table 1. In the BEV group, 6 patients were treated with carboplatin, paclitaxel, and bevacizumab, whereas 7 patients were treated with carboplatin, pemetrexed, and bevacizumab. In the non-BEV group, 11 patients received carboplatin plus paclitaxel, and 1 patient received carboplatin plus pemetrexed.

The response rates for overall disease were 54% in the BEV group and 8% in the non-BEV group ($p = 0.01$; Table 2). The disease control rates for overall disease were 100% in the BEV group and 50% in the non-BEV group ($p = 0.01$; Table 2). The response rates for bone metastases were 23% in the

BEV group and 0% in the non-BEV group (p = 0.038; Table 3). The disease control rates for bone metastases were 100% in the BEV group and 67% in the non-BEV group (p = 0.01; Table 3).

The Kaplan-Meier curve for B-TTP is shown in Fig. 1. The median B-TTPs were 13.7 months in the BEV group and 4.3 months in the non-BEV group (p = 0.06). The Kaplan-Meier curve for TTP is shown in Fig. 2. The median TTPs were 5.7 months in the BEV group and 2.6 months in the non-BEV group (p = 0.17). Overall disease progression was observed in 12 of 13 patients in the BEV group and in all patients in the non-BEV group. The median OS was 6.6 months (range, 4.0–34.7 months) in the non-BEV group and this was not reached (range, 6.6 months–) in the BEV group (p = 0.13). In the present study, the median follow-up duration was 15.1 months.

SREs occurred in 3 patients (23%) in the BEV group and in 6 patients (50%) in the non-BEV group (Table 4). The types of SREs were as follows: 3 instances of the need for bone radiation and 1 instance of spinal cord compression in the BEV group and 5 instances of the need for bone radiation, 1 bone surgery, and 1 pathologic fracture in the non-BEV group.

Discussion

To the best of our knowledge, the present study is the first report to evaluate the bone-specific efficacy of chemotherapy in patients with bone metastases from NSCLC. In addition, it was important to evaluate the bevacizumab-mediated potentiation of chemotherapeutic efficacy against bone metastases. In the present study, in the BEV group, the response and disease control rates for bone metastases were 23% and 100%, respectively, and the median B-TTP was 13.7 months.

Rosen et al. reported a Phase 3 trial of zoledronic acid [10, 21]. Among 254 patients who received zoledronic acid 4 mg, 124 patients (49%) had NSCLC and 207 patients (82%) received chemotherapy. The best bone response rate as per the original criteria was 8%, and the disease control rate for bone metastases was 29%. In this study, by using the RECIST guideline (version 1.1), the response rate for bone metastases was 0% and the disease control rate for bone metastases was 67% in the non-BEV group. In contrast, the response rate for bone metastases was 23% and the disease control rate for bone metastases was 100% in the BEV group. Although different bone lesion response criteria were used for the Phase 3 trial of zoledronic acid and this study, administration of bevacizumab-containing chemotherapy showed some potential for eliciting an effect on bone metastases. In the same Phase 3 trial, the median B-TTP of patients who received zoledronic acid 4 mg was 145 days, and the proportion of patients with at least 1 SRE over a period of 9 months was 38%. In this study, the median B-TTPs were 130 days in the non-BEV group and 412 days in the BEV group. In terms of the proportion of patients

with SREs, 50% of patients in the non-BEV group and 23% of patients in the BEV group had SREs until the first progression of overall disease or the last follow-up visit. These results suggest that bevacizumab-containing chemotherapy specifically controlled bone lesions as well as systemic lesions.

The antitumor activity of bevacizumab-containing chemotherapy is believed to be the result of enhanced chemotherapy delivery to tumor cells [15]. Bevacizumab distribution to bone was similar as that to other organs in ex vivo biodistribution analysis [16]. Inhibiting VEGF-VEGFR-2 signaling inhibited bone metastasis in animal models of lung cancer with bone metastasis [18]. Solares et al. reported a patient with lung adenocarcinoma and bone metastases in whom a complete response was achieved with carboplatin, paclitaxel, and bevacizumab [22]. Paule et al. reported that 2 patients with renal cell carcinoma (RCC) and bone metastases who were treated with the anti-VEGFR inhibitor sunitinib experienced long-term survival and stabilization of bone metastases [23]. They concluded that VEGF-targeted agents such as sunitinib may be effective treatments for bone metastases. Furthermore, a retrospective analysis reported that sunitinib plus bisphosphonates such as zoledronic acid and pamidronate improved the response rate, PFS, and OS in cases of RCC with bone metastases [24]. In our study, the response rates for bone metastases were 23% in the BEV group and 0% in the non-BEV group. These results might validate the clinical efficacy of bevacizumab-containing chemotherapy against bone metastases.

This study has several limitations. The sample size was small. This was a retrospective study

with an inherent potential for bias. The collection of clinical characteristics and treatment response data was retrospective, and the follow-up interval for physical examinations was indefinite. Therefore, future studies are warranted to investigate larger sample sizes.

In conclusion, this study indicates that bevacizumab might potentiate the antitumor activity of chemotherapy against both systemic disease and bone metastases, thereby prolonging bone-specific TTP and reducing the incidence of SREs.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Figure legends

Fig 1.

Kaplan–Meier plot of time to progression of bone metastases (B-TTP) of patients who received chemotherapy containing bevacizumab (BEV group) or lacking bevacizumab (non-BEV group). The median B-TTPs were 13.7 months in the BEV group and 4.3 months in the non-BEV group ($p = 0.06$).

Fig 2.

Kaplan–Meier plot of time to progression of overall disease (TTP) of patients who received chemotherapy containing bevacizumab (BEV group) or lacking bevacizumab (non-BEV group). The median TTPs were 5.7 months in the BEV group and 2.6 months in the non-BEV group ($p = 0.17$).

Table 1 Patients characteristics and chemotherapy regimens

		BEV	non-BEV	P value
Number		13	12	-
Age	median (range)	63 (35–75)	67 (40–76)	0.3255
Sex	M/F	11/2	9/3	0.5476
Smoking	Yes/No	11/2	7/5	0.1394
PS	0/1/2	3/9/1	0/11/1	0.9530
EGFR	Mt/Wt/unknown	4/9/0	2/5/5	0.4054
Regimen of chemotherapy	CBDCA+PTX	-	11	-
	CBDCA+PEM	-	1	
	CBDCA+PTX+BEV	6	-	
	CBDCA+PEM+BEV	7	-	

Mt, mutation; Wt, wild type; CBDCA, carboplatin; PTX, paclitaxel; PEM, pemetrexed; BEV, bevacizumab

Table 2 Response and control rates for overall disease

Best response	BEV (n = 13)	non-BEV (n = 12)	P value
PR	7	1	
SD	6	5	
PD	0	6	
Response rate	54%	8%	0.01
Disease control rate	100%	50%	0.01

PR, partial response; SD, stable disease; PD, progressive disease

Table 3 Response and control rates for bone metastases

Best response	BEV (n = 13)	non BEV (n = 12)	P value
PR	3	0	
SD	10	8	
PD	0	4	
Response rate	23%	0%	0.04
Disease control rate	100%	67%	0.01

PR, partial response; SD, stable disease; PD, progressive disease

Table 4 Proportion of patients with SREs until the first documented event of disease progression

	BEV n = 13	non BEV n = 12
SREs*	3 (23%)	6 (50%)
Radiation to bone	3	5
Surgery to bone	0	1
Spinal cord compression	1	0
pathologic fracture	0	1

SRE; skeletal-related events

*P = 0.16

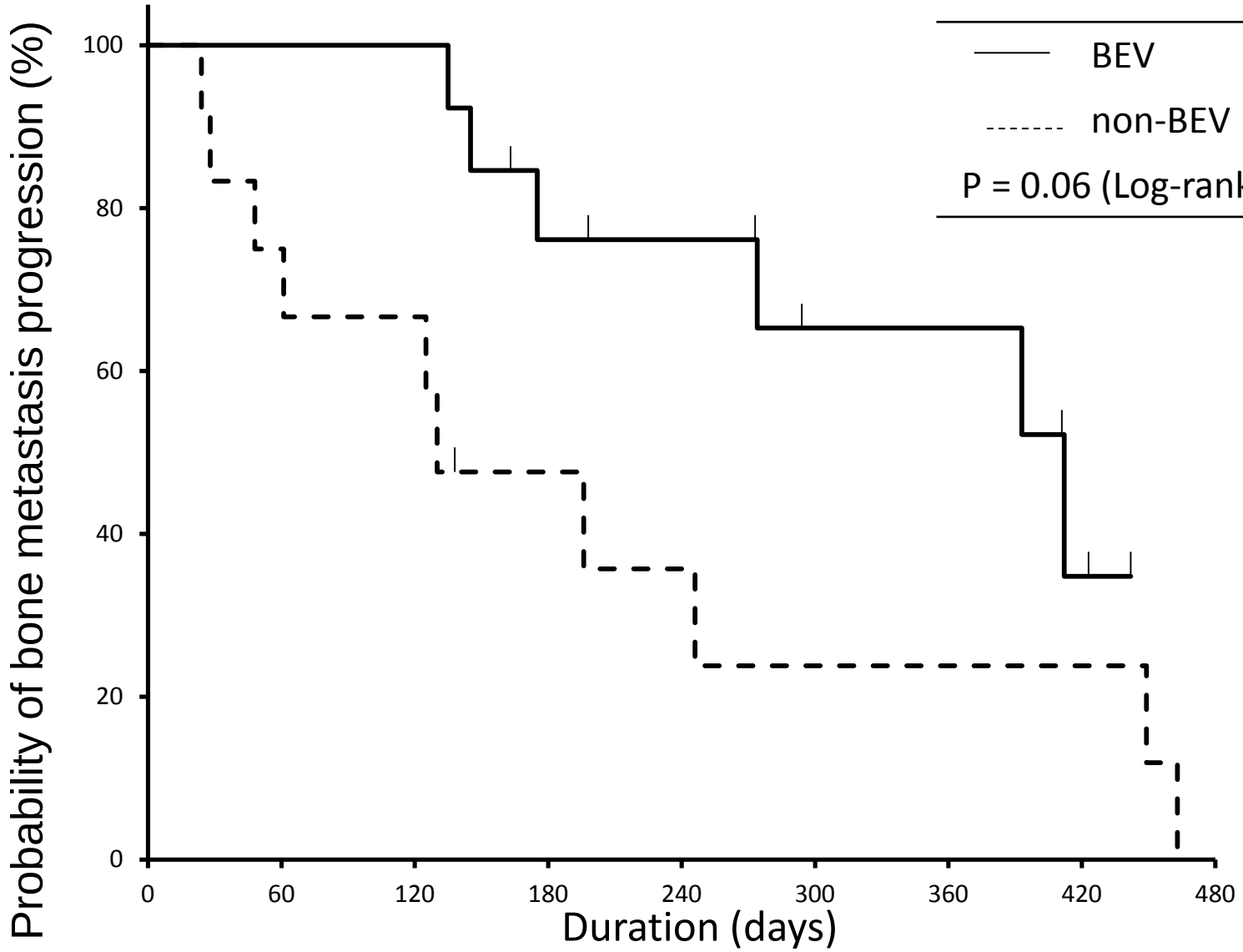

Fig. 1 Time to progression of bone metastases

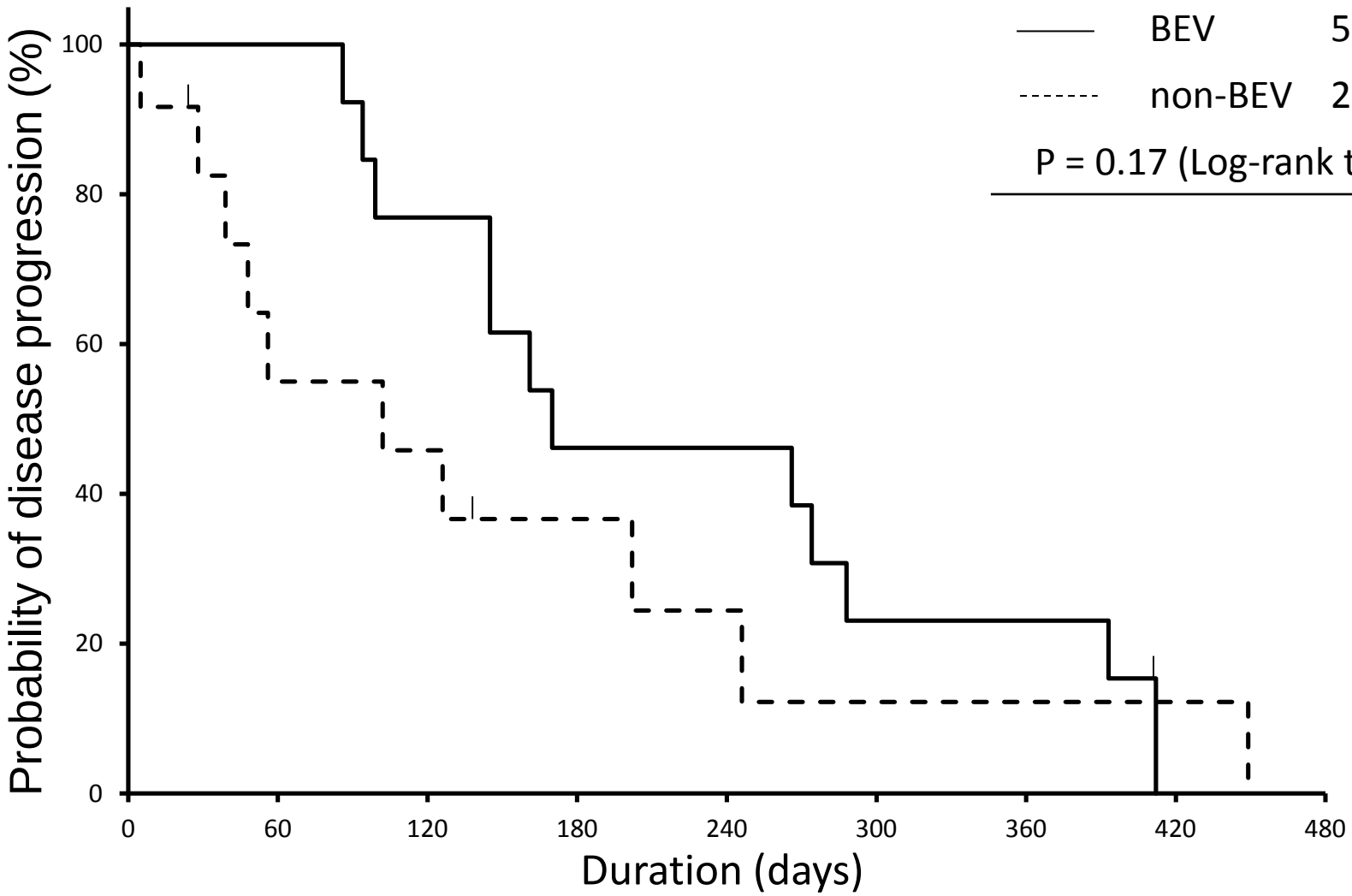

Fig. 2 Time to progression of overall disease