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ORIGINAL ARTICLE

Risk factors for skeletal-related events in non-small cell lung cancer patients treated with bone-modifying agents

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Abstract

Purpose The risk factors for skeletal-related events (SREs) among non-small cell lung cancer (NSCLC) patients during treatment with bone-modifying agents (BMAs) are not yet well-understood.

Methods The medical records of 238 consecutive NSCLC patients treated with BMAs, including zoledronic acid and denosumab, at the Chiba University Hospital from 2012 to 2016 were reviewed in the present study. SREs were defined as either pathologic fractures, spinal cord compression, the need for bone irradiation or surgery, or hypercalcemia. The risk factors for earlier occurrence of the first SRE from the time of the first bone metastasis diagnosis after the initiation of BMA treatment were identified.

Results Of the 238 included patients, 92% ($n = 220$) had a performance status (PS) of 0–2 at diagnosis of bone metastasis. Forty-eight (20%) patients developed at least one SRE. The most common first SRE was the need for bone irradiation surgery ($n = 27$, 56%). Significant risk factors included poor PS (hazard ratio [HR]: 4.36; $p = .024$), male sex (HR: 2.17; $p = .022$), and the use of zoledronic acid (HR: 1.91; $p = .032$). The overall survival (OS) from the first bone metastasis diagnosis was 394 days (95% confidence interval [CI]: 331–465). The OS of patients with PS 3 and 4 at the diagnosis of bone metastasis (median: 36 days; 95% CI: 13–50) was significantly ($p < 0.0001$) shorter than that of patients with PS 0–2 (median: 411 days; 95% CI: 354–558) (HR: 4.53; 95% CI: 2.62–7.35).

Conclusions Careful observation is needed for patients with the identified risk factors, which include poor PS and male sex, despite the BMA treatment.

Keywords Skeletal-related event · Bone-modifying agent · Bone metastasis · Non-small cell lung cancer · Risk factor

Background

Bone is one of the most common sites for metastases from non-small cell lung cancer (NSCLC) [1, 2]. Approximately one-third of the patients with advanced NSCLC experience bone metastases, and more than half of them experience skeletal-related events (SREs) over the course of their disease. These SREs include pathologic fractures, spinal cord compression, the need for bone irradiation or surgery, and hypercalcemia [3, 4]. In addition to worsening patients' quality of life (QOL) [5, 6], SREs also decrease their survival [7]. Therefore, specific treatments for bone metastases are potentially of great clinical benefit for NSCLC patients with bone metastases.

A multidisciplinary approach is essential for the effective management of patients with bone metastases [8, 9]. For instance, bone-modifying agents (BMAs) (e.g., zoledronic acid [10] and denosumab [11]) have shown significant efficacy that delayed the effects of SREs among patients with solid cancers (e.g., NSCLC) and a good performance status. Many guidelines recommend BMAs for all NSCLC patients

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with bone metastases [12–14]. There is one report on the incidence of SREs among NSCLC patients with bone metastases who received zoledronic acid therapy in a clinical setting [15]. Additionally, the risk factors of SREs among NSCLC patients with bone metastases have been reported [16, 17]. However, little has been reported regarding the risk factors of SRE among NSCLC patients with bone metastases during BMA treatment. Since the approval of denosumab, great advancements were made regarding treatment options, such as tyrosine kinase inhibitors (TKIs) and novel immune checkpoint inhibitors. Therefore, the clinical courses may have changed significantly as well since the publication of previous reports. Identifying these risk factors is important when considering BMAs indications and for predicting SREs. This would allow both patients and physicians to have more awareness regarding SREs, highlighting the importance of early treatment initiation and the maintenance of patients' QOL.

Therefore, we conducted a retrospective study to investigate the risk factors associated with the earlier occurrence of the first SRE in NSCLC patients treated with BMAs.

Materials and methods

Study populations

We retrospectively reviewed the medical records of consecutive NSCLC patients who had been treated with BMAs (either zoledronic acid or denosumab) between 2012 and 2016 at the Chiba University Hospital, Chiba, Japan. We chose this period for the following reasons: (1) denosumab was approved in Japan in early 2012; (2) since 2017, the clinical setting in Japan has changed significantly given that immune checkpoint inhibitors were made available as the first-line therapy; and (3) a sufficient observation period was required to adequately detect an event. Patients received either a minimum of 4 mf of zoledronic acid (dose adjusted for renal impairment) through a 15-min IV infusion every 3–4 weeks or 120 mg of denosumab through subcutaneous injections every 4 weeks in accordance with the Japanese regulatory authorities' approved dosage. A multidisciplinary team led by the attending physician and including both orthopedic surgeons and radiation oncologists discussed the approach (e.g., radiotherapy, surgery, or systemic therapy) to the management of (a) cancer pain, (b) imminent danger of pathologic fractures, and (c) spinal cord compression.

Although several trials, especially those investigating prostate and breast cancers, have recently utilized the composite endpoint of symptomatic skeletal events (SSEs) [18], SREs have been widely adopted for NSCLC [8, 9, 16, 17] and were comparable each other. Therefore, we also adopted SREs as events in the present study. SREs were defined as pathologic fractures, spinal cord compression, the need for bone irradiation or surgery, or hypercalcemia. Radiotherapies, including palliative radiotherapy, and bone fractures before treatment with the BMAs were defined as "prior palliative radiotherapy to the bone" and a "prior bone fracture," respectively. Findings from the discharge summaries, physician progress notes, radionuclide and radiographic bone scans, Fludeoxyglucose-Positron Emission Tomography/Computed Tomography (FDG-PET/CT) and other imaging studies, surgical procedure notes, radiation treatment summaries or records, and pathology reports were investigated to track the development of bone metastases or SREs. Multiple variables were assessed, including patient demographic characteristics, histology types (i.e., non-squamous with the driver gene mutation, non-squamous without the driver gene mutation, and squamous), disease status (i.e., metastatic and recurrent), timing of bone metastasis diagnosis, number of bone metastases, hematologic measures at BMA initiation, Eastern Cooperative Oncology Group (ECOG) performance status (PS) when the bone metastases were diagnosed, type of BMAs (i.e., zoledronic acid and denosumab), and the histories of either prior bone fractures or prior palliative radiotherapy to the bone before the initiation of BMAs.

Statistical methods

Descriptive statistics for the clinical and demographic characteristics of all patients were reported. The primary event was the time to the first SRE [9, 14], defined as the time from the first bone metastasis diagnosis to the first SRE that developed after the initiation of BMA treatment. The primary outcome was the identification of the risk factors associated with the earlier occurrence of the first SRE, which was investigated using univariate and multivariate Cox proportional hazards regression analyses. The overall survival (OS) was plotted using the Kaplan–Meier method and compared using the log-rank test. All the analyses were exploratory in nature. A two-sided p value < 0.05 was statistically significant. All statistical analyses were performed using EZR10 version 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [19].

Results

Patient screening

Out of 261 patients screened, 23 were excluded either due to BMA treatment for their hypercalcemia ($n = 20$), absence of metastases but direct invasion of the bone ($n = 2$), or insufficient records or data ($n = 1$). Consequently, the number of patients included in the analysis was 238 (Fig. 1).

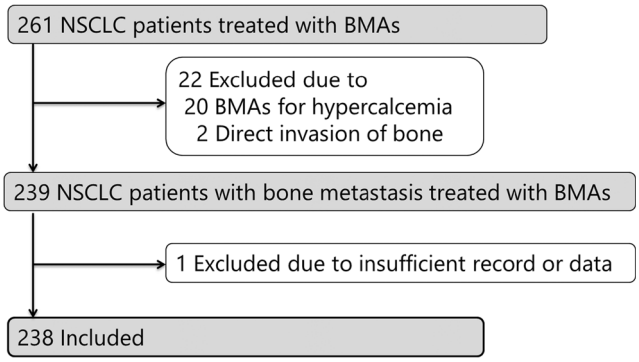

Fig. 1 Patient flow chart showing the numbers of non-small cell lung cancer patients treated with bone-modifying agents, including zoledronic acid and denosumab, at the Chiba University Hospital from 2012 to 2016. NSCLC, non-small cell lung cancer; BMA, bone-modifying agent

Patient characteristics

The baseline patient characteristics are summarized in Table 1. The median duration of patients' follow-up (date of primary bone metastasis diagnosis to the date of the last visit or death) was 287 days (range: 1–3030). In contrast, the median time to the development of metastatic bone disease from the diagnosis of primary NSCLC was 15 days (range: − 98–5710; the negative value indicates that metastatic bone cancer was detected before the diagnosis of NSCLC). At the time of reporting, 77 (32%) of the 238 patients had died; the average time between NSCLC diagnosis and the last visit or death was 440 days (range: 7–5852).

BMA use

For the initial BMA dose, zoledronic acid and denosumab were administered to 118 (50%) and 120 (50%) of the included patients, respectively. Subsequently, 6 (5%) of the 118 patients were switched from zoledronic acid to denosumab, while 4 (3%) of the 120 patients were switched from denosumab to zoledronic acid. The median time from the first bone metastasis diagnosis to the start of BMA treatment was 21 days (range: 0–346), whereas the median duration of BMA treatment was 121 days (range: 0–2905; 0 indicates that BMAs were administered only once). At the time of reporting, 216 (91%) BMA discontinuations were recorded.

Time to the first SRE

The median time from bone metastasis diagnosis to the first SRE was 311 days (range: 22–5831). Over the course of the study period, 48 (20%) patients experienced at least one new SRE. The most frequent SRE was palliative radiotherapy to the bone (n = 27, 14%) (Table 2). The median time from the first BMA dose to the first SRE following treatment initiation was 97 days (range: 0–1537). Multivariate Cox regression analysis indicated that the significant baseline risk factors for the occurrence of the first SRE included male sex (hazard ratio [HR]: 2.17; p = .0022), ECOG PS 3 and 4 (HR: 4.36; p = .0024), and zoledronic acid use (HR: 1.91; p = .032) (Table 3).

Overall survival

Of the 238 included patients, 167 (70%) died. The overall survival (OS) from the first bone metastasis diagnosis was 394 days (95% confidence interval [CI]: 331–465). OS by PS at the diagnosis of bone metastases were as follows: 860 days (95% CI: 559–1568), 412 days (95% CI: 351–598), 188 days (95% CI: 122–290), 36 days (95% CI: 13–50), and 36.5 days (95% CI: 8–78) for PS 0, 1, 2, 3, and 4, respectively. The OS of patients with PS 3 and 4 (median: 36 days; 95% CI: 13–50) was significantly shorter ($p < 0.0001$) than that of patients with a PS 0–2 (median: 411 days; 95% CI: 354–558) (HR: 4.53; 95% CI: 2.62–7.35) (Fig. 2).

Discussion

To the best of our knowledge, this is the first study to include NSCLC patients with bone metastases treated with BMAs in a clinical setting and the natural history of bone metastases from NSCLC. The present study suggested poor PS, male sex, and the use of zoledronic acid to be risk factors for the earlier development of SREs. Furthermore, patients with PS 3 or 4 who were treated with BMAs had significantly shorter survival.

First, we found that patients with a PS of 3 or 4 at the time of bone metastasis diagnosis had a significantly greater risk of an earlier occurrence of the first SRE than those with a PS of 0–2. Overall, 84% of patients on zoledronic acid included in phase III study had a PS of 0–2 [10], and all patients on denosumab included in the phase III study had a PS of 0–2[11]. Thus, for patients with a PS of 3 or 4, the benefit of BMAs was uncertain based on these trials. We hypothesize the following reasons behind the occurrence of earlier events in patients with poor PS: (1) given that systemic therapy is not usually recommended for patients with poor PS, especially when driver gene alterations are not present [14, 20], doctors are more likely to promptly offer palliative radiation; (2) furthermore, the overall response rates of tyrosine kinase inhibitors in patients with poor PS and driver gene alterations were reported to be lower than the rates seen in patients with good PS [21, 22]. Therefore, the former are more likely to fail to control their disease with tyrosine kinase inhibitors; and (3) as a rationale for the above argument and as we have shown in our paper, patients with poor PS had a significantly shorter OS, which may have led to earlier disease progression and the occurrence of events. Our finding suggests that patients with poor PS should be closely monitored. Another risk factor for

Table 1 Clinical characteristics of non-small cell lung cancer patients with bone metastases treated with bone-modifying agents at the time of bone metastasis

Characteristics	All patients (n = 238)
Age at diagnosis, years, median (range)	67.2 (33.7–92)
Sex, n (%)	
Male	153 (64)
Female	85 (36)
Smoking status, n (%)	
Smoker	152 (64)
Never smoked	68 (15)
Performance status, n (%)	
0	38 (16)
1	138 (58)
2	44 (18)
3	14 (6)
4	4 (2)
Pathology and driver-gene mutation status, n (%)	
Non-squamous with EGFR mutation/ALK fusion	76 (32)
Non-squamous without EGFR mutation/ALK fusion	125 (53)
Squamous	36 (15)
Disease status, n (%)	
Primarily metastatic	159 (67)
Recurrent metastatic	79 (33)
Timing of bone metastases diagnoses, n (%)	
At initial staging	136 (57)
During follow-up	102 (43)
Number of bone metastases, n (%)	
Single	69 (29)
Multiple	169 (71)
Prior palliative radiotherapy to the bone, n (%)	
Yes	90 (38)
No	148 (62)
Prior bone fracture, n (%)	
Yes	90 (38)
No	148 (62)
Type of BMA, n (%)	
Zoledronic Acid	118 (50)
Denosumab	120 (50)

NSCLC non-small cell lung cancer, *BMA* bone-modifying agent, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase

earlier SRE development, as shown by our findings, was male sex. Sekine et al. also reported that male sex was an independent risk factor for the development of SREs in 2009 [16]. However, biological explanations of the male sex being a risk factor for earlier SREs are difficult to prove, considering that osteoporosis and pathological fractures are more common among women than men, both in Japan [23] and globally [24]. One possible hypothesis is that differences in the response to systemic treatment might have influenced such findings. Women with advanced NSCLC were reported to survive

Table 2 Frequency and type of skeletal-related events

Type of SREs	First SRE n (%)		Subsequent SREs n (%)		Total
Pathological fracture	6	(3)	0	(0)	6
Spinal cord compression	8	(3)	2	(1)	10
Required for palliative radiotherapy to bone	27	(14)	2	(1)	29
Required for surgery to bone	0	(0)	0	(0)	0
Hypercalcemia of malignancy	7	(3)	1	(< 1)	8
Total	48	(20)	5	(2)	53

SRE skeletal-related event

No patients developed three or more SREs

Table 3 Univariate and multivariate analyses of the time from bone metastasis to the first skeletal-related event

		Univariate			Multivariate		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Age (year)	< 75	1			-		
	> = 75	1.35	0.69–2.66	0.382			
Sex	Female	1			1		
	Male	1.83	0.98–3.45	0.058	2.17	1.12–4.22	0.022
Smoking status	Never smoked	1			-		
	Smoker	1.62	0.88–2.97	0.121			
Histology type	Non-Sq mutation +	1			-		
	Non-Sq mutation −	2.28	1.18–4.40	0.014			
	Squamous	2.48	0.99–6.22	0.054			
Disease status	Recurrent metastatic	1			-		
	Primary metastatic	1.02	0.56–2.88	0.940			
PS	0–2	1			1		
	3, 4	3.74	1.11–12.6	0.033	4.36	1.21–15.69	0.024
Timing of bone metastases diagnosis	At initial diagnosis	1			-		
	During follow-up	1.37	0.77–2.42	0.281			
Number of bone metastases	Multiple	1			-		
	Single	1.39	0.76–2.53	0.280			
LDH (U/L)	< 240	1			-		
	≥ 240	1.45	0.81–2.59	0.214			
Ca (mg/dL)	< 10.2	1			-		
	≥ 10.2	2.28	1.09–4.77	0.028			
Prior palliative radiotherapy to the bone	Yes	1			-		
	No	1.12	0.62–2.02	0.616			
Prior bone fracture	No	1			-		
	Yes	1.76	0.75–4.17	0.197			
Type of BMA	Denosumab	1			1		
	Zoledronic acid	1.94	1.08–3.48	0.026	1.91	1.06–3.45	0.032

Sq squamous cell carcinoma; mutation +, driver-gene mutation (EGFR mutation/ALK fusion) positive; mutation −, driver-gene mutation negative; *PS* performance status, *BMA* bone-modifying agent

longer than men both before and after the development of EGFR-TKIs [25, 26]. Given that the majority of SREs are induced by disease progression, the male sex may not be a specific risk factor for earlier SREs but a risk factor for earlier disease progression instead. In the present study, we reported treatment with zoledronic acid as a risk factor for earlier SRE development. However, this may be the result of a bias present in this study. Specifically, a total of 773 patients were randomized to receive either zoledronic acid or the placebo in the study phase III for the assessment of zoledronic acid as a treatment of skeletal metastases in patients with NSCLC and other solid tumors. Results suggested that zoledronic acid significantly delayed the median time to the first SRE ($p = 0.009$) [10]. On the other hand, a total of 1776 patients were randomized to receive either denosumab or zoledronic in the study phase III for the assessment of denosumab as a treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancers). Results indicated denosumab to be noninferior to zoledronic acid in delaying the time to the first in-study SRE (HR: 0.84; 95% CI: 0.71–0.98; $p = 0.0007$); however, the former was not significantly superior to the latter ($p = 0.06$, adjusted for multiplicity). By tumor stratification factors, the effect of denosumab on the time to the first in-study SRE in patients with NSCLC did not significantly differ from that seen in patients who received zoledronic acid (HR: 0.84; 95% CI: 0.64–1.10; $p = 0.20$) in a previous study [11]. Therefore, our findings from a cohort of 238 patients are not powerful enough to suggest the superiority of denosumab over zoledronic acid. A retrospective single-centered cohort study of Japanese people suggested that denosumab was superior to zoledronic acid in terms of OS [27]. However, a later larger phase III study did not find a significant improvement in OS among those who received denosumab [28]. This discrepancy is possibly induced by the differences in the start dates of

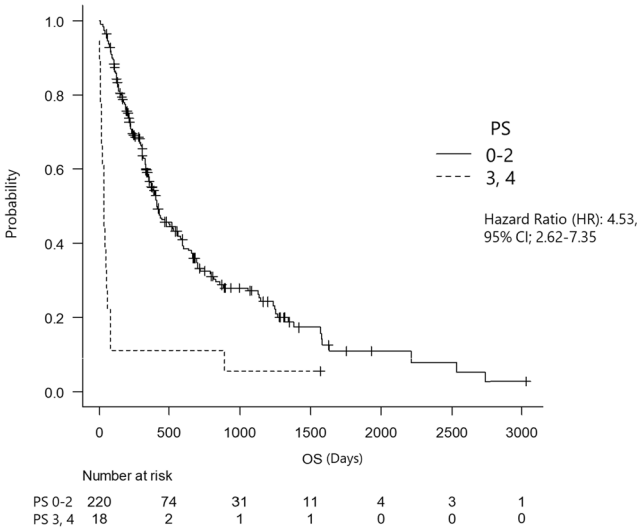

Fig. 2 Overall survival for non-small cell lung cancer patients with bone metastases treated using bone-modifying agents. OS was significantly affected by the performance status. OS, overall survival; PS, performance status

agents' administration. While authorities in Japan approved the use of zoledronic acid for preventing SREs in 2006, denosumab was only approved in 2012. In our study, patients who were treated with BMAs between 2012 and 2016 were included; therefore, it is possible that patients who received denosumab benefited from newer, more effective therapies. Overall, all the identified risk factors for earlier SREs are possibly related to the survival prognosis. Thus, physicians should also pay more attention to the occurrence of early SREs in patients who are expected to have early disease progression.

Over a median follow-up period of 9 months, 20% of patients experienced at least one new SRE. This rate was relatively low compared with that reported in previous retrospective studies from clinical settings [15, 16]. These discrepancies might be a result of the following factors. First, improvements have been made to the sensitivity of the diagnostic modality for bone metastases. During the study period, we performed FDG-PET/CT as a staging procedure for almost all metastatic NSCLCs. In a meta-analysis, the superiority of FDG-PET/CT was shown over FDG-PET, MRIs, and bone scintigraphy [29]. It is possible that FDG-PET/CT revealed bone metastases with a low potential for SREs. Second, there has been an increase in the use of opioids in Japan [30]. As described in a previous report [17], palliative radiotherapy to the bone was also the most common SRE identified among NSCLC patients with bone metastases in this study. The main aim of palliative radiotherapy to the bone is to control pain [31].

Our study suggests that the survival prognosis among patients with bone metastases has improved compared to that reported in previous studies [4, 29]. However, among those with a PS of 3 or 4, the survival prognosis was significantly shorter, with a median duration of only 36 days from the diagnosis of bone metastases. As previously reported in the 2015 [4], the prognosis among patients with a poor PS at the diagnosis of bone metastasis is poor. Since phase III studies of zoledronic acid and denosumab were conducted, many evolutional treatment options have been established, such as EGFR, ALK, ROS1 TKIs, and immune checkpoint inhibitors. Importantly, the inclusion criteria for many of those evolutional prospective interventional studies were limited to patients with a PS of 0 or 1, with the exception of small studies on gefitinib [21], alectinib [22], pembrolizumab [32], and nivolumab [33]. Therefore, few standard treatment options are available for patients with a poor PS. For this reason, BMA treatment should be carefully considered for patients with a poor PS, especially for those without an indication for treatment.

The limitation of this study will now be highlighted. First, given that this was a retrospective conducted at a single institution, the generalizability of our findings may have been impacted. Second, the sample size was small, potentially limiting the validity of our findings. Third, pain evaluation with either BPI or other tools was not conducted in the present study. Therefore, the number of events which may impact patients' quality of life remains to be determined in future studies. Finally, we included patients treated with various strategies due to the differences in treatment timing.

Conclusion

This retrospective study showed that, among patients with bone metastases from NSCLC, those who either had a poor PS, were male, or were treated with zoledronic acid were more likely to develop SREs earlier. Therefore, such high-risk patients should be closely monitored.

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Data collection: Go Saito, Tsukasa Ishiwata, Ichiro Yoshino, Yuichi Takiguchi, and Koichiro Tatsumi

Statistical analyses: Go Saito, Takahiro Ebata, Tsukasa Ishiwata, and Shunichiro Iwasawa

Interpretation of the data: All authors

Drafted and finalized the manuscript: All authors

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest Dr. Saito reports personal fees from AstraZeneca, during the conduct of the study, personal fees from Chugai

Pharmaceutical, and personal fees from Ono Pharmaceutical, outside the submitted work; Dr. Iwasawa reports personal fees from Daiichi Sankyo Company, Limited, personal fees from AstraZeneca K.K., personal fees from Bristol-Myers Squibb K.K., personal fees from MSD K.K., grants and personal fees from Ono Pharmaceutical Co., Ltd., during the conduct of the study, and personal fees from Chugai Pharmaceutical Co., Ltd., outside the submitted work; Dr. Takiguchi reports grants and personal fees from Novartis, grants from Daiichi Sankyo, personal fees from AstraZeneca, during the conduct of the study, grants and personal fees from Eli Lilly, grants and personal fees from Chugai Pharmaceutical Co., grants and personal fees from MSD, grants from Takeda, grants and personal fees from Taiho Pharmaceutical Co., grants from Kyowa-Hakko Kirin, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical Co., and grants and personal fees from Bristol Meyers Squib, outside the submitted work; Dr. Ebata, Dr. Ishiwata, Dr. Yoshino, and Dr. Tatsumi have nothing to disclose.

Ethics approval and consent to participate The institutional review board of the Chiba University Hospital approved the study protocol (approval no.2634).

Consent to participate Given the retrospective nature and the anonymous design of our study, written informed consent was not obtained from patients, who were however provided with the opportunity to opt out of their confidential patient information being used for research using our institutional website.

Consent for publication We provided all patients with the opportunity to opt out of their confidential patient information being used for research using our institutional website.

Code availability Not applicable.

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