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Original Paper

Does Supportive Pamidronate Treatment Prevent or Delay the First Manifestation of Bone Metastases in Breast Cancer Patients?

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The effect of pamidronate treatment on the first development of bone metastases was investigated in 124 patients with breast cancer, with either locally advanced disease ($n = 33$) or extraskeletal metastases ($n = 91$), but no bone metastases in a randomised, multicentre, open controlled study. Patients were assigned to treatment with oral pamidronate, 300 mg/day, ($n = 65$) or to a control group ($n = 59$). Tumour therapy was freely allowed. A first clinical event of skeletal morbidity occurred in 22% pamidronate and 20% control patients; unequivocal first radiological manifestation of bone metastases was found in 36% pamidronate and 27% control patients (n.s.). The actuarial risk of a first skeletal event was similar in both groups. Quality-of-life measurements of bone metastases-related aspects showed no differences between the two groups. 19 patients withdrew from the study because of gastrointestinal complaints attributed to pamidronate. We conclude that supportive oral pamidronate treatment (300 mg/day) does not prevent nor delay the development of bone metastases in breast cancer patients at risk.

Key words: bisphosphonates, pamidronate, breast cancer, bone metastases
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INTRODUCTION

BREAST CANCER patients with metastases developing first in extraskeletal sites (about 60% at the time of first diagnosis of disseminated disease) have an estimated chance of about 50% of developing bone metastases [1–3]. Furthermore, patients presenting with locally advanced breast cancer (UICC stage III) have a high relapse rate; in a recent study distant metastases developed in 70–80% of patients and the median relapse-free survival and overall survival were 2 and 4 years, respectively [4]. Once the disease spreads, 70% of these patients will eventually develop clinically manifest bone metastases. Therefore, breast cancer patients with extraskeletal metastatic disease and patients with locally advanced disease are at high risk of suffering during their limited survival time, from impairment of their quality of life due to events of skeletal morbidity such as bone pain, pathological fractures and hypercalcaemia. In previous studies, we and others have shown that long-term supportive bisphosphonate treatment reduces significantly skeletal morbidity in patients with breast cancer and established metastatic bone disease [5–8], and improves selective aspects of quality-of-life [9]. The question arises whether bisphosphonate treatment, initiated in the bone metastases-free stage of disease, can prevent or delay the development of bone involvement.

In this paper, we report effects of long-term pamidronate treatment on the first manifestations of bone metastases. We assessed clinical and radiological parameters of bone

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metastases; a quality-of-life survey was also performed. This study was designed similarly to and conducted simultaneously with the earlier reported study of supportive pamidronate treatment of patients with breast cancer and bone metastases [7,9].

PATIENTS AND METHODS

Patients

This was an open, randomised study involving 124 patients with breast cancer and either established extraskeletal metastases ($n = 91$), or locally advanced disease ($n = 33$) but no bone metastases at study entry. Locally advanced disease was defined as UICC stage IIIb (TNM classification, 1987 edition); however, patients with a T1–3N1–2 M0 tumour and histologically proven positive apical axilla nodes were also included.

Patients were randomly assigned, per participating centre (9 in total), to pamidronate treatment ($n = 65$) or to a control group ($n = 59$). Trial participation ended with death, pamidronate toxicity or on patient request. Treatment was intended to be lifelong. Patients with hypercalcaemia, peptic ulcer, malabsorption, creatinine clearance ≤ 30 ml/min, and life expectancy ≤ 6 months were not included in the study. The study was approved by the ethical committees of the participating centres and informed verbal consent was obtained from all patients.

Treatment

Pamidronate was given as enteric coated tablets of 150 mg, to be taken with water twice daily 30 min before meals. The study was originally planned with a dose of 600 mg/day. In view of the high incidence of gastrointestinal toxicity with this dose in our earlier reported study [7], the dose was reduced to 300 mg/day. However, 6 of the 65 patients in the present study used 600 mg/day and these are included in the intention-to-treat analysis. Concomitant tumour therapy was not restricted to ensure optimal treatment of changing clinical needs. The pamidronate tablets were prepared by the pharmacy of the University Hospital Leiden.

Investigations

Clinical data and blood for blood count, creatinine, alkaline phosphatase, calcium, phosphate, albumin and live enzymes were collected every 3 months. Patients were also asked to complete a quality-of-life questionnaire every 3 months. The questionnaire contained 17 items, grouped into four categories: bone pain, mobility impairment, gastrointestinal toxicity and fatigue. The method of the quality-of-life survey has been previously reported in detail [9]. The clinical data were collected from the patient's files by data managers from regional Comprehensive Cancer Centres; the coordination of the data management and the quality-of-life surveys was carried out by the Comprehensive Cancer Centre West, The Netherlands.

At entry into the study, every 6 months thereafter, and at any time of clinical suspicion of metastatic bone involvement, a bone scintigram was performed. In case of abnormalities, skeletal radiographs of the areas of increased isotope uptake were made to specify the nature of the scintigraphic findings. Basal bone scans and, if necessary, additional skeletal radiographs were reviewed centrally to confirm the absence of bone metastases at the time of entry in the study. Consecutive investigations were reviewed for the first development of bone metastases by two expert readers blinded for clinical data.

Response criteria

The analysis focused only on the first manifestation of bone metastases. For that, clinical as well as radiological parameters were used. Clinically, we defined the event-free-period (EFP) as the time from randomisation until the first skeletal event. Then we calculated the actuarial risk (cumulative incidence) of a first skeletal event. The latter is the single or simultaneous occurrence of the following events of skeletal morbidity during a 3-month period: hypercalcaemia (serum calcium ≥ 2.75 mmol/l), severe bone pain requiring radiotherapy or surgery, (impending) pathological fracture treated with radiotherapy or surgery, and change of systemic therapy (chemotherapy or endocrine) for bone metastases as the dominant indication. In accordance with commonly used criteria, impending fractures were defined as: in long bones, osteolytic lesions greater than 2 cm with $\geq 50\%$ cortical destruction and symptomatic with bone pain; in vertebrae, evident increased radionuclide uptake on bone scintigraphy and/or $\geq 50\%$ osteolysis of vertebral body and arch associated with severe, localised pain. Radiologically, we defined freedom-from-progression (FFP) as the time from randomisation until the first manifestation of bone metastases on the bone scintigraphy and/or on radiographs; the actuarial risk of the first radiological bone involvement was then calculated. If a scintigraphic abnormality preceded the confirmation on radiographs, the time of the first evidence on the bone scan determined the FFP. Overall survival is the period from randomisation until death while on study or until the end of the observation period. The quality-of-life analysis focused on changes over time in the scores for the four categories. At each follow-up, patients scored the items on a 4-point scale, ranging from none = 0 to very severe = 3. Then, for every category, the item scores were averaged.

Statistical methods

The two groups were compared by the *t*-test or Mann–Whitney test for quantitative variables and the chi-square test for qualitative variables. Survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test. Risk factors were simultaneously tested in a multivariate analysis by the Cox regression model for their independent influence on the EFP. The sample size was calculated on the assumption of a 30% difference in the incidence of bone metastases and/or prolongation of disease-free interval by 3 months or more ($\alpha = 0.05$, $\beta = 0.20$). With 10% non-evaluable patients, the study required 50 patients per arm. For the quality-of-life analysis, trends over time of the scores of the four categories evaluated were estimated using a multivariate repeated measurements MANOVA model [10]. These estimated time trends were then tested for differences between the two groups. Censoring, mortality and withdrawal from the study do not violate the assumptions underlying this method of analysis [9].

RESULTS

65 pamidronate and 59 control patients with comparable characteristics were included in the trial (Table 1).

Trial participation ended with death in 14 pamidronate and in 26 control patients after a median observation period of 16 and 20 months, respectively. The median follow-up of the living patients (51 pamidronate and 33 control) was 19 and 34 months, respectively. This difference is due to early withdrawal of 15 patients on pamidronate because of gastrointestinal complaints. Consequently, the number of patients partici-

Table 1. Patient characteristics at time of trial entry

	Pamidronate	Control
Number	65	59
Female/male	65/0	58/1
Median age (years)		
At primary diagnosis (range)	57 (27–81)	53 (35–87)
At randomisation	61	56
Oestrogen receptor status		
Positive	34	31
Negative	16	15
Unknown	15	13
Extraskeletal metastatic disease		
Visceral (and soft tissue)	29	28
Soft tissue only	20	14
Locally advanced disease	16	17
Time period (months)(mean)		
Primary diagnosis to first metastasis	42	33
First metastasis to randomisation	14	14
Primary diagnosis to randomisation*	1.4	1.8
Previous systemic treatment†		
Chemotherapy	7	11
Endocrine therapy	14	10
Both	10	2
None	36	36
Systemic treatment at study entry		
Chemotherapy	15	16
Endocrine therapy	31	20
None	19	23

*Applies only to locally advanced breast cancer patients. †≥ 1 course of systemic treatment before trial entry. None of the differences between the two groups were statistically significant.

Table 2. Risk (cumulative incidence) of first events

	Risk of first clinical event		Risk of first radiological event	
	Pamidronate	Control	Pamidronate	Control
At study start	$n = 65$	$n = 59$	$n = 36$	$n = 44$
At 12 months				
number at risk	36	41	24	32
actuarial %	7	6	13	10
At 24 months				
number at risk	17	27	7	20
actuarial %	23	22	38	29
At 36 months				
number at risk	6	18	3	11
actuarial %	50	28	60	29
	$P = 0.57$		$P = 0.15$	

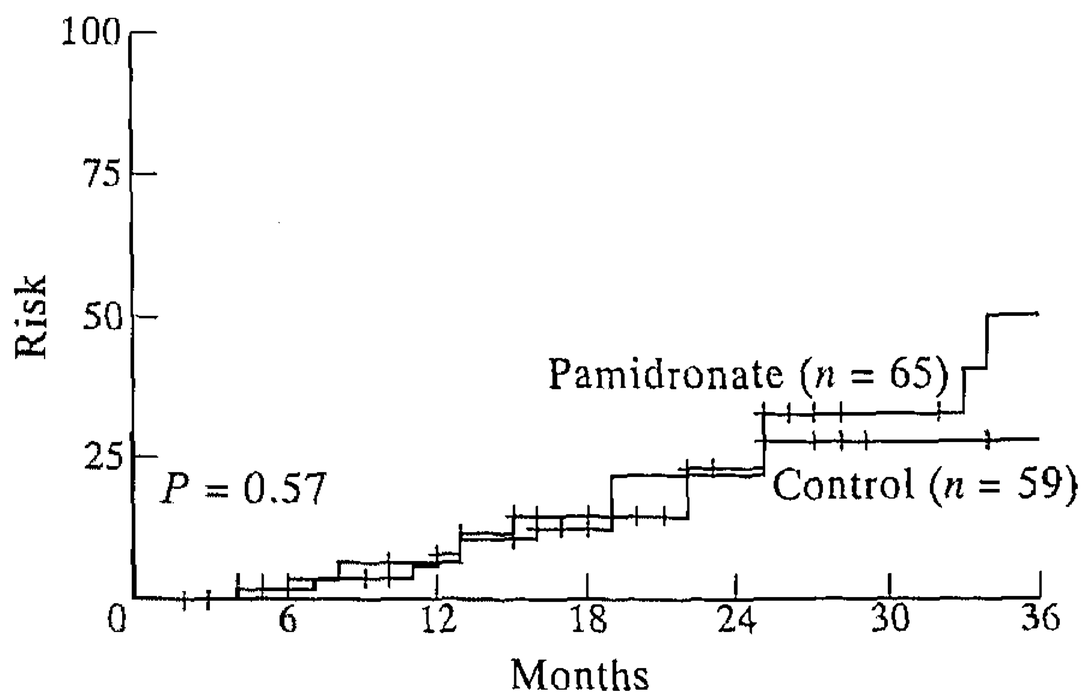

Figure 1. Risk (cumulative incidence) of first clinical skeletal event; $P = 0.57$.

pating in the study beyond 36 months of follow-up was too small for reliable group comparisons and the analysis was restricted to an observation period of 36 months. In addition to these early withdrawals, 19 pamidronate and 5 control patients ended trial participation on request for various reasons (4/19 pamidronate patients because of gastric intolerance), often after long observation periods.

Analysis of clinical parameters

14 of 65 (22%) pamidronate and 12 of 59 (20%) control patients developed a first skeletal event during the follow-up. The median time to first bone event was not reached in either group within the 36 months of the analysis. The presenting events of morbidity were two hypercalcaemic episodes, 12 changes of systemic therapy, and one radiotherapy for bone pain in the pamidronate group. In the control group, the first clinical events of bone metastases were two hypercalcaemic episodes, eight changes of systemic therapy, four radiotherapy for bone pain, and one surgery for pathological frature. Presenting events occurred simultaneously in 1 pamidronate patient compared to 3 control patients. When the actuarial risk of a first skeletal event was compared, no significant difference was found between the two groups, $P = 0.57$ (Table 2, Figure 1).

We assessed a number of risk factors for their independent contribution to the EFP: age ≤ 50 or > 50 years, locally advanced or extraskeletal metastatic disease, oestrogen receptor status and the presence of visceral metastases. None of these factors was found to have a major impact on the EFP ($P = 0.23$–0.95). Overall survival was not significantly different, $P = 0.30$; the 3-year survival was 58% in the pamidronate and 55% in the control group.

Analysis of radiological parameters

At the end of the study, bone scans and skeletal radiographs from the four major contributing hospitals, covering 102 (82%) of the studied patients, were reviewed centrally. On review, 36% of pamidronate and 27% of control patients had unequivocal scintigraphical and radiological evidence of first manifestation of bone metastases. The risk of a first radiological manifestation of bone metastases was similar in both groups, $P = 0.15$ (Table 2, Figure 2). It is well known that

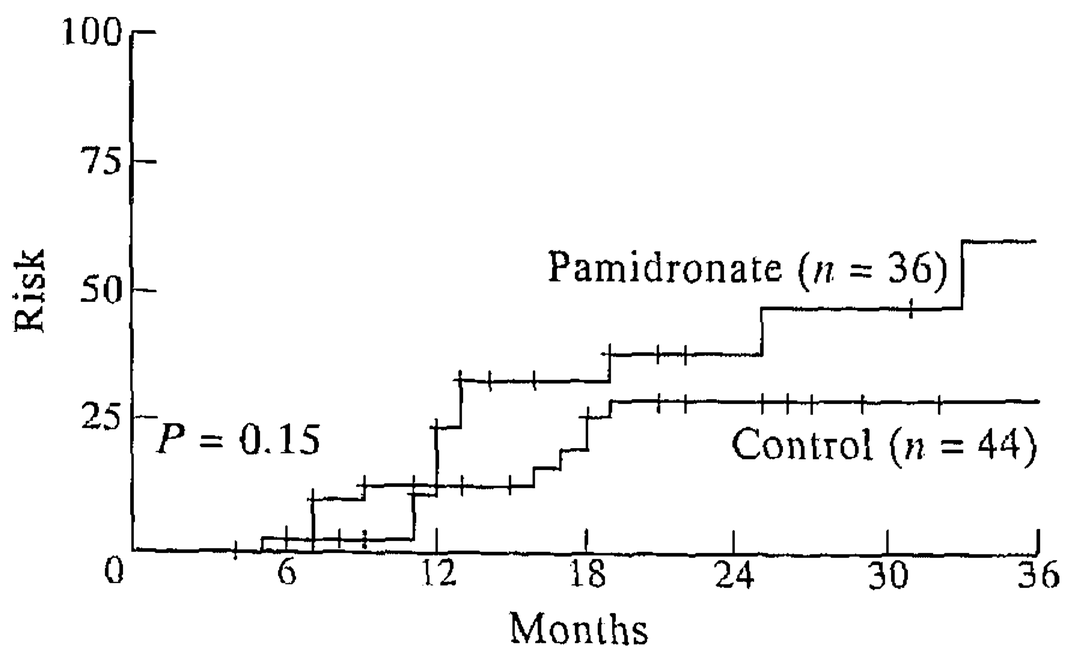

Figure 2. Risk (cumulative incidence) of first radiological skeletal event: a comparison of 36 pamidronate patients and 44 control patients; $P = 0.15$.

bone scintigraphy has a high sensitivity but low specificity for the detection of bone metastases in breast cancer. Indeed, scintigraphic abnormalities were present in 30 patients at trial entry, but skeletal radiographs of these regions eliminated bone metastases in 29 patients; in one case, the presence of two osteolytic lesions at the time of trial entry were confirmed retrospectively. The patient was included in the analysis. When the analysis was restricted to the patients with a strictly normal bone scan at trial start, there was still no difference in the risk of radiological development of bone metastases (35% of pamidronate patients and 28% of control patients, $P = 0.40$).

Quality-of-life

Completed questionnaires were evaluable from 49 pamidronate and 41 control patients. At baseline, the mean scores of the two groups for the mobility impairment, bone pain and gastrointestinal toxicity categories were comparable, but pamidronate patients showed a worse score for fatigue of 0.60, compared to 0.30 for the control group. During follow-up, a significant worsening in the trend over time was found for the scores for mobility impairment, from 0.54 to 0.95 in the pamidronate and control groups alike, and gastrointestinal toxicity, from 0.20 to 0.45 in the pamidronate group and from 0.14 to 0.40 in the control group. However, for both categories, the worsening over time was similar in the two groups, $P = 0.87$ and 0.88, respectively. The scores for bone pain and fatigue did not change significantly over time and there was no effect of pamidronate treatment.

DISCUSSION

Previous studies have reported extensively on the efficacy of bisphosphonate treatment on skeletal morbidity in patients with breast cancer [5–8]. In the present study, we assessed the ability of long-term supportive treatment with oral pamidronate 300 mg/day to prevent the first manifestation of bone metastases in patients with an increased risk to develop metastatic bone disease. Our results show that pamidronate in the dose and mode of administration used had no significant effect. Compared to controls, there was no evidence of a prevention nor of delay of the first manifestation of metastatic bone disease assessed both by clinical and radiological parameters. Also, several risk factors known to influence the pattern of metastasis or prognosis were tested, but none was found to interact with pamidronate efficacy. Furthermore, the quality-of-life survey revealed comparable scores and trends over time for the bone metastases-related domains—bone pain and mobility impairment—in both pamidronate and control patients. This merely confirms the clinical and radiological findings. The observed incidence of clinical events related to bone metastases was lower than that of radiological changes. Furthermore, both were lower than expected from historical data; 50% in extraskeletal metastatic breast cancer and 70% in locally advanced disease [1–4]. These differences may be because, for the clinical data, we focused on the occurrence of severe, quality-of-life impairing skeletal events rather than on complaints from bone metastases because in our opinion the reduction of skeletal morbidity by palliative, supportive treatment should have major clinical impact which can be objectively assessed. Furthermore, less than half of the patients reached the end-point of their disease, i.e. death, during the observation time. A number of patients either withdrew from the study or participated in the study until the time of this analysis. Obviously, bone metastases that developed after this time were not analysed. Last but not least, due to changing therapies of early breast cancer, the pattern of metastasis may change [11].

Previous *in vivo* animal studies suggested that prophylactic treatment with bisphosphonate clodronate in metastasis-free animals protects the skeleton against tumour-induced osteolysis [12]. However, the present study failed to show any effect of pamidronate at the dose and mode of administration used on the first manifestation of bone metastasis. Reasons for this lack of an effect, which contrasts with the beneficial effect of pamidronate in metastatic bone disease, need to be considered. Tumour properties, such as the production of bone resorbing factors and interactions between invading tumour cells and adjacent tissues, may differ for breast cancer associated with active bone metastases compared to breast cancer with only extraskeletal metastases. Furthermore, there may be an effect of bisophosphonate dose and distribution. In the presence of active skeletal lesions, the bisphosphonate will concentrate preferentially in areas of enhanced bone resorption, i.e. the metastases. In the absence of active skeletal lesions, the drug will concentrate in any area of the skeleton undergoing remodelling, resulting in a more general distribution. It may be that areas of developing metastatic osteolysis are inadequately protected, perhaps even more so at lower doses of the bisphosphonate. This is supported by our earlier finding that the pamidronate efficacy to reduce skeletal morbidity was dose-dependent and 300 mg/day clearly was less effective than 600 mg/day [7]. The negative results of the present study do not exclude the possibility that the bisphosphonate may be effective when given intravenously [13], but this may be difficult in a preventive setting. Alternatively, other newer potent bisphosphonates which can be given in effective doses without causing gastrointestinal toxicity may have a favourable effect [14].

Toxicity of treatment is of great importance when palliation is the objective. In 19 patients (15 early and another 4 later in the study) the occurrence of nausea and vomiting, and stomatitis in one case, was attributed to pamidronate treatment resulting in withdrawal from the study. In contrast to these clinical findings, the quality-of-life survey did not detect a difference in the level of gastrointestinal complaints between pamidronate and control patients. As reported earlier by us [7, 9], primary gastrointestinal intolerance does occur, usually within weeks after the start of treatment. Similar complaints may also occur later in the course of the disease, but then they seem to associate more with advanced disease- and prognosis-related factors rather than with pamidronate treatment. The lack of placebo treatment in our controls carried the risk of attributing preferentially the gastrointestinal symptoms to the test drug.

In summary, in the present study, we found no beneficial effect of long-term pamidronate treatment at a dose of 300 mg/day, on delaying or preventing metastatic bone involvement in breast cancer patients at risk of developing bone metastases.

1. Elte JWF, Bijvoet OLM, Cleton FJ, van Oosterom AT, Sleeboom HP. Osteolytic bone metastasis in breast carcinoma: pathogenesis, morbidity and bisphosphonate treatment. *Eur J Cancer Clin Oncol* 1986, 22, 493–500.
2. Lee Y-TM. Patterns of metastasis and natural courses of breast carcinoma. *Cancer Metastasis Rev* 1985, 4, 153–72.

3. Koenders PG, Beex LV, Langens R, *et al.* Steroid hormone receptor activity of primary human breast cancer and pattern of first metastasis. The Breast Cancer Study Group. *Breast Cancer Res Treat* 1991, **18**, 27–32.
4. Rubens RD, Bartelink H, Engelsman E, *et al.* Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. *Eur J Cancer Clin Oncol* 1989, **25**, 667–678.
5. Elomaa I, Blomqvist C, Gröhn P, *et al.* Long-term controlled trial with diphosphonate in patients with osteolytic bone metastases. *Lancet* 1983, **i**, 146–149.
6. Paterson AHG, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993, **11**, 59–65.
7. Van Holten-Verzantvoort ATM, Kroon HM, Bijvoet OLM, *et al.* Palliative pamidronate (APD) treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993, **11**, 491–98.
8. Van Holten-Verzantvoort ATM, Bijvoet OLM, Cleton FJ, *et al.* Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* 1987, **ii**, 983–985.
9. Van Holten-Verzantvoort ATM, Zwinderman AH, Aaronson NK, *et al.* The effect of supportive pamidronate treatment on aspects of quality of life of patients with advanced breast cancer. *Eur J Cancer* 1991, **27**, 544–9.
10. Winer BJ. *Statistical Principles in Experimental Design.* New York, McGraw Hill, 1971.
11. Kamby C, Ejlertsen B, Andersen J, *et al.* The pattern of metastasis in human breast cancer. Influence of systemic adjuvant therapy and impact on survival. *Acta Oncol* 1988, **27**, 715–719.
12. Krempien B, Manegold Chr. Prophylactic treatment of skeletal metastases, tumour-induced osteolysis, and hypercalcaemia in rats with the bisphosphonate C12MBP. *Cancer* 1993, **72**, 91–98.
13. Conte PF, Latreille J, Mauriae L, Koliren L, Ford JM. Aredia infusions in breast cancer: a randomized phase III trial to assess delay in progression of bone metastases. *Bone Miner* 1994, **25**, S78.
14. Papapoulos SE, van Holten-Verzantvoort ATM. Modulation of tumour-induced bone resorption by bisphosphonates. *J Steroid Biochem Mol Biol* 1992, **43**, 131–136.

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