



Phase II study of docetaxel and carboplatin as second-line treatment in NSCLC[☆]

Floris M. Wachters^{a,*}, John W.G. van Putten^b,
H. Marike Boezen^c, Harry J.M. Groen^a

^a Department of Pulmonary Diseases, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

^b Department of Pulmonary Diseases, Martini Hospital, P.O. Box 30.033, 9700 RM Groningen, The Netherlands

^c Department of Epidemiology and Statistics, University of Groningen, P.O. Box 196, 9700 AD Groningen, The Netherlands

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Summary Aim of this study was to evaluate activity and toxicity of docetaxel and carboplatin as second-line treatment in advanced non-small-cell lung cancer (NSCLC) patients who failed or relapsed after previous chemotherapy. Patients had to have unresectable stage IIIb or IV NSCLC, previous chemotherapy, a performance status ≤ 2 , a normal bone marrow reserve, and an adequate renal and liver function. Treatment consisted of docetaxel 75 mg/m² and carboplatin AUC 6 mg/ml min administered every 3 weeks for a maximum of 5 cycles. Fifty-seven patients with a median age of 57 years were included. Prior treatment consisted of gemcitabine alone ($n = 2$) or gemcitabine in combination with cisplatin ($n = 26$) or epirubicin ($n = 29$). Median number of cycles for carboplatin and docetaxel was 4. Granulocytopenia and thrombocytopenia common toxicity criteria (CTC) grades 3 and 4 occurred in 79 and 30% of patients, respectively. Febrile neutropenia occurred in eight patients (14%), of whom two patients died. Fatigue grades 2 and 3 occurred in 42% of patients. Other non-haematological toxicity was mild. Tumour response rate was 37%, irrespective of the previous regimen. Median survival was 31 weeks, 1-year survival was 32%. In conclusion, the combination of docetaxel and carboplatin is active as second-line treatment in platinum and non-platinum pre-treated patients.

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1. Introduction

Meta-analysis of studies on metastatic non-small-cell lung cancer (NSCLC) have shown improvement of survival with the use of chemotherapy [1]. This has recently been confirmed for stage IIIb as well as stage IV disease by large randomised trials [2,3]. Despite the small benefits, the American Society

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* Corresponding author. Tel.: +31-50-3612357;
fax: +31-50-3619320.

E-mail address: f.m.wachters@int.azg.nl (F.M. Wachters).

of Clinical Oncology recommends to offer systemic chemotherapy to patients with advanced NSCLC who have an acceptable performance status [4]. However, most patients will eventually relapse after a previous tumour response. In stage IIIb disease, most patients have received prior chemotherapy and radiotherapy, and generally have a good performance status when they relapse. Due to occurrence of somewhat higher response rates in stage IV disease with the use of newer anticancer agents, time to progression will often be slightly longer, and therefore more patients recover from previous chemotherapy. Also, patients with a good performance status who fail to respond to first-line treatment frequently request additional therapy. Consequently, an increasing number of patients with stages IIIb and IV NSCLC will expect to be treated with second-line chemotherapy.

Until today, second-line treatment in advanced NSCLC is only recently investigated. Older-generation drugs such as etoposide, vindesine, epirubicin and cisplatin are active as single-agents in previously untreated NSCLC, but do not achieve response rates over 10% when used in second-line setting [5]. The activity of new cytotoxic drugs such as gemcitabine, vinorelbine and paclitaxel in second-line setting is not well defined [5–12]. Most promising experience in second-line chemotherapeutic treatment of NSCLC is with docetaxel, which in phase II studies showed favourable tumour responses ranged from 16 to 22% [13–15]. However, a randomised study with docetaxel at a dose of 75 mg/m² compared to best-supportive care showed a lower response rate (7%), but still a significant improvement in survival and quality of life, without an excess of toxicity [16]. Comparison with vinorelbine or ifosfamide as second-line treatment was also in favour of docetaxel [17]. Based on these results offering second-line chemotherapy in NSCLC is advocated and docetaxel is often used as reference regimen.

Platinum-containing doublets are nowadays considered standard as first-line treatment of NSCLC. A meta-analysis comparing first-line treatment with combination chemotherapy to single-agents in metastatic NSCLC has shown a nearly two-fold increase in response rate and a modestly superior survival for combination chemotherapy, at the cost of an increase in toxicity [18]. Whether doublets should be the treatment of choice for second-line treatment is unknown. Only limited data on the activity of platinum-containing doublets in platinum and non-platinum pre-treated patients is available. We were interested in the activity of the combination of docetaxel and carboplatin as second-line treatment in NSCLC patients, who were treated

with platinum or non-platinum-containing regimens as first-line therapy. In chemotherapy-naïve patients the combination of docetaxel and carboplatin was active with response rates between 27 and 44%, and acceptable toxicity [19–22].

Primary endpoint of the study was tumour response rate. Secondary endpoints were toxicity and survival. Additionally, the effects of prior chemotherapy, prior tumour response, and treatment interval on the efficacy were studied.

2. Patients and methods

2.1. Patient selection

Patients were included if they had a relapse or progressive disease of pathologically proven stage IIIb or IV NSCLC during or after prior chemotherapy. Prior treatment with taxoids was not permitted. Prior radiotherapy was allowed as long as it had been completed at least 4 weeks prior to inclusion in the study, the patient had recovered from any side effect, and disease progressed outside the radiation field. All patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 . An adequate bone marrow reserve with leukocytes $\geq 3.0 \times 10^9 \text{ l}^{-1}$, neutrophils $\geq 1.5 \times 10^9 \text{ l}^{-1}$, platelets $\geq 100 \times 10^9 \text{ l}^{-1}$ and haemoglobin $\geq 10.0 \text{ g/dl}$ was required. Measurable or evaluable tumour lesions on physical examination, chest X-ray, or CT-scan were necessary. Patients had to take contraceptive precautions, and females with childbearing potential had to have a negative pregnancy test.

Patients were excluded if they had active infections or current symptomatic brain metastases. Patients were also excluded if they had inadequate liver function (defined as serum bilirubin $\geq 35 \mu\text{mol/l}$ and/or serum alanine aminotransferase and serum aspartate aminotransferase more than three times the upper limit of normal), impaired renal function (defined as a serum creatinine $\geq 130 \mu\text{mol/l}$ or creatinine clearance $\leq 60 \text{ ml/min}$), or uncorrected hypercalcaemia. Patients with a second primary malignancy, except carcinoma in situ of the cervix or adequately treated basal cell carcinomas of the skin or adequately treated upper respiratory tract malignancies, were excluded. Patients with peripheral polyneuropathy common toxicity criteria (CTC) grade 2 or more were also excluded.

The protocol was approved by the local medical ethics committee. Informed consent was obtained from all patients. No other chemotherapy

or experimental medication was permitted while patients were on study.

3. Treatment schedule and dose modifications

Docetaxel was administered at a dose of 75 mg/m² by a 1 h intravenous infusion. Afterwards carboplatin was given as a 30 min intravenous infusion. The area under the concentration–time curve (AUC) used for carboplatin was 6 mg/ml min and the dose of carboplatin was calculated according to the Chatelut formula [23]. Both agents were administered every 3 weeks, on an outpatient basis. Treatment consisted of a maximum of 5 cycles and was stopped earlier in case of tumour progression, intolerable toxicity, or patient's wish. Antiemetics were ondansetron 8 mg twice a day on the infusion day and two subsequent days, and dexamethason 8 mg which was given orally 12 h before and 12 h after docetaxel infusion, and intravenously 30 min before infusion. This also prevents hypersensitivity reactions caused by docetaxel.

Drug administration was postponed to a maximum of 2 weeks if there was incomplete haematological recovery on day 22 (neutrophils $<1.5 \times 10^9 \text{ l}^{-1}$ and/or platelets $<100 \times 10^9 \text{ l}^{-1}$), or in case of persistent CTC grade 2 or more non-haematological toxicity (except alopecia). The dose of docetaxel for subsequent cycles was reduced to 75% in case of a nadir of leukocytes below $1.0 \times 10^9 \text{ l}^{-1}$ or platelets below $25 \times 10^9 \text{ l}^{-1}$ for at least 10 days, thrombocytopenia associated with bleeding, or febrile neutropenia. In case of recurrent CTC grade 4 thrombocytopenia the carboplatin dose was adjusted to AUC = 5 mg/ml min. Treatment was stopped in case of CTC grade 3 or 4 non-haematological toxicity.

4. Treatment evaluation

Toxicity was measured according to the CTC of the National Cancer Institute. Complete blood cell counts were performed before each infusion, and at day 12 of each cycle. On day 1 of each cycle, patient evaluation also included liver and renal functions, ECOG performance status, toxicity scoring, and imaging tests to assess tumour response. Tumour response was measured according to standard World Health Organisation (WHO) criteria [24]. After discontinuation of treatment patients were evaluated every 6 weeks with physical ex-

amination, laboratory tests, chest X-ray, and additional imaging tests on clinical indication to assess tumour progression.

5. Statistical analysis

Response rate was the primary end point. The true response rate was estimated to be more than 12%. A critical minimal value of 4% was used. A true response rate below this 4% would clearly imply that the treatment regimen is not effective, whereas a true response rate above 12% would imply that the treatment regimen has therapeutic efficacy that would warrant further investigation. We will test the null hypothesis that the true response rate is less than 4% versus the alternative hypothesis that the true response rate is more than 12%. Using Fleming's single stage design [25], with a one-sided 0.05 alpha level of falsely rejecting the null hypothesis, a total of 56 patients was required [7].

All patients who received at least one cycle of treatment were analysed for response, toxicity and survival. Fisher's exact test was used to compare response rates in different groups according to stage, prior chemotherapy regimen, treatment interval, and response to prior treatment. Median survival and median progression-free survival were calculated from the start of second-line treatment and were analysed according to the Kaplan–Meier method. The log-rank test was used to detect differences in survival between groups according to tumour response, performance score, prior treatment, treatment interval, and response to first-line treatment. Treatment interval was defined as the time between the end of first-line treatment till the start of second-line treatment. To identify potential prognostic factors, a multivariate analysis was performed using a logistic regression model for response rate and a Cox regression model for survival. A $P < 0.05$ was considered statistically significant.

6. Results

6.1. Patient characteristics

From January 1999 until June 2001, 57 patients were included. The median age of these patients was 57 years (range 30–77), the median ECOG performance score was 1 (range 0–2). The majority of patients (88%) had stage IV disease. Baseline characteristics are shown in Table 1. For further analysis the two patients treated with single-agent gemc-

Table 1 Baseline characteristics at the start of second-line treatment

Sex	
Male	36
Female	21
Age (years)	
Median (range)	57 (30–77)
Histology	
Squamous cell carcinoma	19
Adenocarcinoma	28
Large cell carcinoma	10
Stage	
IIIb	7
IV	50
Performance status	
0	18
1	32
2	7
Prior chemotherapy	
Cisplatin–gemcitabine	26
Epirubicin–gemcitabine	29
Single-agent gemcitabine	2
Response to prior chemotherapy	
Complete response	1
Partial response	32
Stable disease	17
Progressive disease	7
Interval after previous treatment (weeks)	
Median (range)	20 (2–100)

itabine as first-line treatment will be considered as having received a non-cisplatin combination. Response rate to first-line chemotherapy was 58%. Eight patients also had received additional high-dose thoracic radiotherapy, with a mean (range) dose of 56 (50–60) Gy.

7. Treatment and toxicity

The median (range) number of cycles per patient was 4 (1–5). A total of 203 cycles of carboplatin and docetaxel were administered. The maximum number of 5 cycles was completed by 37% of patients. Reasons for treatment discontinuation were tumour progression (30%), haematological toxicity (9%), non-haematological toxicity (11%), patients request (9%), and early death (5%). Early death occurred in two patients with febrile neutropenia and in one patient with tumour progression.

During treatment the dose of docetaxel had to be reduced to 75% in six patients (11%). The carboplatin dose was reduced to AUC = 5 mg/ml min in

Table 2 Worst haematological CTC toxicity grade (percentage of patients)

	CTC grade			
	1	2	3	4
Anemia	47	23	7	2
Leukopenia	9	12	37	32
Granulocytopenia	5	7	16	63
Thrombocytopenia	14	12	23	7

one patient (2%). The second, third, fourth and/or fifth cycle were postponed for maximally 2 weeks in respectively 17, 31, 41, and 43% of the total number of patients receiving these cycles.

Haematological toxicity is shown in Table 2. The worst toxicities were granulocytopenia and leukopenia. Granulocytopenia CTC grade 3 or 4 occurred in 79% of patients. Eight patients (14%) were hospitalised for febrile neutropenia. Two of these patients died due to septicaemia. Due to granulocytopenia treatment was frequently postponed, reduced, or discontinued. Haematopoietic growth factors were not used. Twenty-one patients (37%) received one or two red blood cell transfusions during treatment. At the study time, erythropoietin was not routinely administered. A platelet transfusion was required in three patients (5%).

Non-haematological toxicity is listed in Table 3. The most frequent non-haematological toxicities were fatigue, alopecia, nausea and neuropathy. The worst toxicities were fatigue and dehydration. CTC grade 3 or 4 fatigue occurred in six patients (11%). Two patients (4%) were hospitalised

Table 3 Worst non-haematological CTC toxicity grade (percentage of patients)

	CTC grade			
	1	2	3	4
Alopecia	32	60	–	–
Arthralgia	7	2	–	–
Constipation	5	–	–	–
Creatinine	–	2	–	–
Dehydration	–	2	2	–
Diarrhoea	7	–	–	–
Edema	4	2	–	–
Fatigue	51	33	9	2
Mucositis	2	4	–	–
Myalgia	11	5	–	–
Nausea	47	4	–	–
Nail changes	5	2	–	–
Neuropathy	35	5	–	–

for dehydration; one patient needed intravenous hydration for persisting nausea, the other patient for persisting diarrhoea.

8. Tumour response

A partial response was achieved in 21 of the 57 patients included in the study, resulting in an overall response rate of 37% (95% CI, 24–49). Twenty patients (35%) had stable disease, and sixteen patients (28%) had progressive disease. The relation between tumour response to second-line treatment, prior treatment regimen, treatment interval, and response to first-line treatment is shown in Table 4. Response rate to docetaxel and carboplatin was not significantly different in patients previously treated with a platinum versus a non-platinum regimen, in patients with a treatment interval between first-line and second-line treatment less versus more than 15 weeks (other intervals also showed no difference), and in responders versus non-responders on first-line therapy. In two out of seven patients (29%) who were progressive during first-line chemotherapy a partial response to docetaxel and carboplatin was observed. Tumour response rate was 43% in patients with stage IIIb compared to 36% in patients with stage IV disease ($P > 0.05$). A logistic regression model using disease stage, histology, gender, age, performance status, first-line treatment regimen, treatment interval, and response to prior treatment as potential predictive factors, failed to identify any

factor being significantly predictive for tumour response.

Out of the seven patients with stage IIIb included in this study, three achieved a partial response. None of these patients received subsequent thoracic radiotherapy since one patient had already been treated with irradiation, another patient had a pulmonary function insufficient for additional radiotherapy, and the third patient was not irradiated due to presence of malignant pleural effusion. At total of seven patients (12%) received third-line chemotherapy.

9. Survival

At December 2002 all patients had died. The median progression-free survival was 17 weeks (95% CI, 9–25). The median survival for all patients was 31 weeks (95% CI, 26–36), the 1-year survival rate (\pm S.E.) was 32% (\pm 6%) (Fig. 1). Median survival time for responding patients was 67 weeks (95% CI, 47–87) versus 22 weeks (95% CI, 10–35) for non-responding patients ($P < 0.01$). Median survival for patients with performance score 0, 1 and 2 was 55 weeks (95% CI, 45–65), 22 weeks (95% CI, 15–30) and 26 weeks (95% CI, 5–47), respectively. Median survival was significantly longer for patients with a performance score of 0 compared to patients with a performance score of 1 or 2 ($P < 0.01$). In the subgroup of patients receiving the maximum of 5 cycles, patients with a performance score of 1 or 2 had a significantly worse survival compared to patients with a performance score of 0 ($P < 0.05$). Survival seemed not related to factors associated with first-line therapy because no significant differences in survival were found between patients previously treated with a platinum versus a non-platinum regimen, between patients with a treatment interval (between first-line and second-line treatment) less versus more than 15 weeks, and between responders and non-responders on first-line therapy (Table 4). Likewise, progression-free survival was not related to the above mentioned factors associated with first-line chemotherapy. A Cox regression model was used to identify independent prognostic factors for survival. The factors disease stage, histology, gender, age, performance status, first-line treatment regimen, response to prior treatment, and treatment interval were used in this model. This model showed that only a performance status >1 was a significant independent prognostic factor for a shorter survival (odds ratio of mortality: 2.6; 95% CI, 1.4–4.9). Overall median survival from start of first-line chemotherapy was 78 weeks (95% CI,

Table 4 Relation between type of first-line treatment, treatment interval and response to first-line treatment vs. response rate and survival after carboplatin and docetaxel

	Response rate (%)	Median survival (weeks) (95% CI)
First-line treatment		
Platinum	31	30 (24–36)
Non-platinum	42	32 (21–44)
Treatment interval		
≤ 15 weeks	32	16 (2–30)
> 15 weeks	40	35 (27–43)
Response first-line treatment		
Complete/partial response	39	33 (27–39)
Stable disease	35	29 (6–53)
Progressive disease	29	16 (15–16)

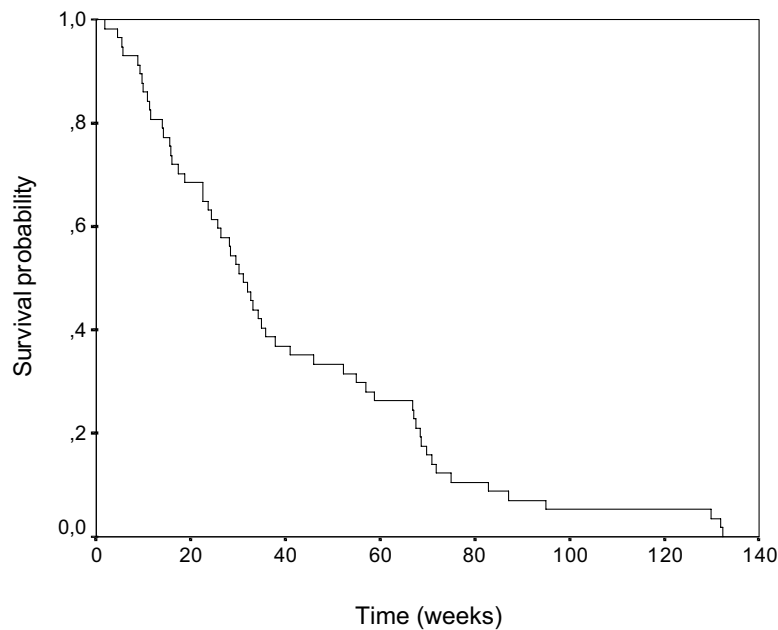


Fig. 1 Kaplan–Meier curve for survival.

65–90), with a one and 2-year survival rate (\pm S.E.) of 75% (\pm 6%) and 26% (\pm 6%), respectively.

10. Discussion

Despite an increasing number of chemotherapeutic agents for NSCLC only a few have shown reproducible antitumour activity in second-line setting. One randomised study, by Shepherd et al., has shown a benefit of second-line treatment with single-agent docetaxel compared to best-supportive care in NSCLC patients. The response rate was 7%, and the median survival improved from 4.6 to 7.0 months [16]. As the results are only marginal it is of particular interest for further studies to evaluate whether a combination of another agent with docetaxel might lead to further improvement for NSCLC patients receiving second-line chemotherapy.

In this trial, activity of docetaxel and carboplatin was shown in previously treated NSCLC patients with a good performance status. The response rate in our study (37%; 95% CI, 24–49) seems very promising and is higher than the reported 16–22% in phase II studies for single-agent docetaxel as second-line treatment [13–15]. Fossella et al. found in a randomised phase III trial response rates of 11 and 7% for single-agent docetaxel 100 and 75 mg/m² every 3 weeks, respectively [17]. Survival and toxicity data were in favour of the docetaxel 75 mg/m² regimen. Taken together, the two phase III studies by Shepherd et al. [16] and Fossella et al.

[17] found, for docetaxel 75 mg/m², a median survival and 1-year survival between 5.7–7.5 months and 32–37%, respectively. In our study this was 7.1 months and 32%, respectively.

Two other trials evaluated the use of docetaxel and carboplatin in previously treated NSCLC patients. A phase I trial by Oka et al. assessed a fixed AUC of 5 mg/ml min of carboplatin in combination with escalating docetaxel doses [26]. Maximum tolerated dose in this trial was 60 mg/m² docetaxel. Response rate of the sixteen patients included in this study was 31% (95% CI, 14–56). Laack et al. performed a pilot study using carboplatin AUC 5 mg/ml min and docetaxel 75 mg/m² every 3 weeks as second-line treatment in 26 patients with metastatic NSCLC [10]. The reported response rate of 19% (95% CI, 7–39) was not significantly different from our response rate, because the confidence intervals were overlapping. The median survival (8.1 months), 1-year survival (26%), and median progression-free survival (3.9 months) were comparable to our results. However, haematological toxicity reported by Laack et al. was less severe. Febrile neutropenia occurred in 4% of patients compared to 14% of patients in our trial. Also, CTC grade 3 or 4 fatigue was more frequently reported in our trial.

Whether second-line treatment should include a platinum-compound has not been solved yet. First-line treatment generally includes a platinum-containing doublet and therefore in second-line treatment this is usually considered unnecessary. Our study suggests that even in

platinum pre-treated patients higher tumour responses occur when platinum is again used in second-line treatment. We found no significant difference in response rate between platinum and non-platinum pre-treated patients. For patients with a relapse of small-cell lung cancer, tumour response can be predicted from treatment interval, response to first-line treatment, and chemotherapeutic agents used in first-line. In the current study, these variables were not found significant predictors of tumour response or survival after second-line treatment. Therefore, the occurrence of cross-resistance between this docetaxel and carboplatin regimen and the first-line gemcitabine-based treatment seems unlikely. This is consistent with Georgoulas [27] who also suggested that the probability to respond to second-line treatment is independent of the response to first-line treatment in NSCLC patients.

Whether other two-drug combinations are superior to single-agent treatment in second-line setting is presently unclear. Second-line treatment with single-agent gemcitabine was reported in two phase II trials to yield a tumour response rate between 6 and 19% and a median survival between 17 and 34 weeks [6,7]. In a Greek trial, the addition of docetaxel to gemcitabine did not result in a superior response rate (16%) or median survival (28 weeks) as compared with the response and survival reported with single-agent docetaxel or gemcitabine in previous trials [28]. However, a recently published Japanese phase II trial conversely reported a higher response rate (28%) and a longer median survival (48 weeks) after second-line chemotherapy with gemcitabine in combination with docetaxel [29]. A similar median survival was reported in a phase II trial in which paclitaxel and gemcitabine were administered in previously treated NSCLC patients [30]. Results of phase III trials with docetaxel or paclitaxel in combination with gemcitabine should be awaited before final conclusions can be drawn.

Recently, two promising novel agents were studied for use in second-line setting in NSCLC patients. Gefitinib, an orally active EGFR tyrosine kinase inhibitor, was studied in a randomised phase II trial [31]. Patients were randomised to receive either 250 or 500 mg gefitinib daily. Antitumour activity, with a response rate between 18 and 19%, as well as symptom relief and improvement in quality of life was reported. Median survival was 7.6 and 8.0 months for the 250 and 500 mg group, respectively. Pemetrexed, a novel multitargeted antifolate, was examined as second-line treatment in NSCLC in a recently presented phase III trial [32]. Patients ($n = 571$) were randomised to receive either peme-

trexed 500 mg/m² or docetaxel 75 mg/m². No significant differences in response rate and survival were found between both arms. However, toxicity in the pemetrexed arm seemed more favourable, with less febrile neutropenia. Response rate and survival in the docetaxel arm were in accordance with other studies using single-agent docetaxel as second-line treatment [16,17]. A phase III trial is required to clarify whether there is a survival advantage for treatment with the combination of docetaxel and carboplatin compared to docetaxel or pemetrexed monotherapy.

11. Conclusion

The combination of docetaxel and carboplatin is active as second-line treatment after prior platinum and non-platinum-based chemotherapy in patients with advanced NSCLC, suggesting non-cross-resistance.

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