Cancer Chemother Pharmacol (2003) 52: 339–345
DOI 10.1007/s00280-003-0601-4

ORIGINAL ARTICLE

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A multicenter phase II study of irinotecan (CPT-11) alternated with 5-fluorouracil and leucovorin as first-line treatment of patients with metastatic colorectal cancer

Received: 6 September 2002 / Accepted: 12 February 2003 / Published online: 8 July 2003

Abstract *Purpose*: In this multicenter phase II study the efficacy and safety of the alternating schedule of irinotecan (CPT-11) with bolus 5-fluorouracil (5-FU) and leucovorin (LV) were assessed as first-line chemotherapy in patients with metastatic colorectal cancer (CRC). *Patients and methods*: Enrolled in the study were 43 patients with advanced CRC. They received CPT-11 350 mg/m^2 i.v. on day 1, alternating with LV 20 mg/m^2 i.v. and 5-FU 425 mg/m^2 i.v. daily for five consecutive days, on days 22–26 (Mayo Clinic regimen). One cycle consisted of 6 weeks. *Results*: A total of 179 cycles were administered with a median of four per patient (range one to nine). Efficacy was analyzed on an intention-to-treat basis. The overall objective response rate was 30% (95% CI 16–44), with four complete responses and nine partial responses, whereas 20 patients (4%) showed stable disease. The median time to disease progression was 9.0 months and median survival was 18.5 months. Grade 3/4 diarrhea was mainly related to CPT-11 rather than to 5-FU (9.3% vs 4.7% of patients), whereas grade 3/4 neutropenia was higher during 5-FU administration (16.3% vs 7.0% of patients). *Conclusions*: The alternating schedule of CPT-11 with 5 days bolus of 5-FU and low-dose LV showed a clinical benefit in terms of tumor growth control as first-line treatment of patients with metastatic CRC. The overall safety data confirmed this alternating combination as a well-tolerated treatment.

Keywords Alternating schedule · Bolus 5-FU · Irinotecan · Advanced colorectal cancer

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Introduction

Irinotecan (CPT-11) and 5-fluorouracil (5-FU) are two drugs currently used for the treatment of colorectal cancer (CRC). 5-FU inhibits the enzyme thymidylate synthase (TS), thus interfering with the formation of new strands of DNA during replication. 5-FU is also incorporated into RNA and DNA, where it inhibits DNA synthesis [26]. 5-FU is known to be active in the treatment of advanced CRC, but most treated patients only survive for approximately 1 year after diagnosis of metastatic disease with an overall response rate of 23% [26]. To improve response rates and survival, researchers have attempted to enhance the efficacy of 5-FU and have also investigated the efficacy of other agents. Approaches have included prolonging administration time (continuous infusion rather than bolus injection) and combining 5-FU with biochemical modulators that alter its biochemical interactions [5, 12, 28]. Calcium leucovorin (LV) is the most extensively studied and widely used biochemical modulator of 5-FU [13]. LV is a reduced folate which, when combined with 5-FU, augments 5-FU cytotoxicity by increasing the inhibition

of TS by the 5-FU metabolite 5-fluoro-2′-deoxyuridine monophosphate. The so-called Mayo Clinic regimen, consisting of a 5-day bolus 5-FU and LV (low dose), is one of the most commonly used regimens. The modulation of 5-FU by LV improves the response rate, but not the median survival, when compared with 5-FU bolus alone [1]. The limiting toxicities are neutropenia and diarrhea [16].

Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin that binds and stabilizes topoisomerase I as it works to uncoil DNA during cell division. This stabilizes the complex inhibitor-enzyme-DNA and stops the progress of replication forks along the DNA, resulting in double-strand DNA breaks and consequent apoptosis. CPT-11 is active in the treatment of advanced CRC, with no cross-resistance to prior 5-FU therapy (with or without LV modulation) and with reported response rates of 15–32% in chemotherapy-naive and 18–27% in 5-FU-pretreated patients [7, 8, 18, 22, 23]. The main toxicities of CPT-11 are well known and documented. An acute cholinergic syndrome is common but can be successfully treated or prevented by the use of atropine, and severe diarrhea has also been reported but early treatment with a high dose of loperamide has notably reduced the need for hospitalization.

The rationale of an alternating schedule is to ensure that full doses of all three agents (CPT-11, 5-FU and LV) could be administered by avoiding the potential incidence of overlapping side effects that may occur with concomitant drug administration. Nevertheless, few studies have been reported using the alternating schedule, some of the data being preliminary results of multicenter studies [2, 21, 29]. These studies suggest that the alternating schedule is a safe and effective first-line regimen against advanced CRC. Recently, a study has shown the effectiveness and tolerability of another alternating schedule in patients with metastatic CRC: CPT-11 and weekly high-dose LV and 48-h 5-FU infusion [19].

The aim of this phase II study was to assess the combination of CPT-11 given in 6-week cycles, alternating with the Mayo Clinic regimen of 5-FU/LV, as first-line treatment of metastatic CRC. The primary efficacy endpoint was the objective response rate. Secondary endpoints were time to disease progression and overall survival.

Material and methods

Selection criteria

The inclusion criteria were the following: (1) histological diagnosis of non-resectable, advanced CRC; (2) one or more bidimensionally measurable target lesions; (3) age between 18 and 75 years; (4) life expectancy >3 months; and (5) a World Health Organization (WHO) performance status (PS) <2. The laboratory data requirements before study entry were as follows: polymorphonuclear neutrophil (PMN) count $>2000/mm^3$, platelet count $>100{,}000/mm^3$, hemoglobin >10 g/dl, serum creatinine level <135 μmol/l, bilirubin level less than 1.25 times the upper normal limit (UNL), AST/ALT level less than 2.5 times the UNL and prothrombin time $>50\%$ unless liver metastases were present, in which case the bilirubin level could be less than 1.5 times the UNL and AST/ALT level less then 5 times the UNL.

The exclusion criteria were the following: (1) previous treatment with CPT-11 or other topoisomerase I inhibitors; (2) more than one previous adjuvant chemotherapy line or any palliative line; (3) potentially resectable metastases; (3) high risk of poor outcome due to concomitant nonmalignant disease (inflammatory enteropathy, major organic failure, chronic diarrhea); (4) severe uncontrolled infection; (5) central nervous system metastases; (6) previous cancer history (except for resolved cervical carcinoma or basal cutaneous carcinoma); (8) bowel obstruction; and (9) lactating or potentially childbearing women. All patients provided their written informed consent and both local regulations and the principles of the Declaration of Helsinki were followed.

Chemotherapy regimen

All patients were treated with CPT-11 at a dose of 350 mg/m^2 given as an i.v. infusion over 30–90 min on day 1 of a 6-week cycle, alternating with 20 mg/m^2 LV given as an i.v. infusion over 15 min, followed immediately by 425 mg/m^2 5-FU given as an i.v. bolus, for five consecutive days (days 22–26) (Fig. 1). Cycles were repeated every 6 weeks. Guidelines for dose modification due to toxicity are shown in Table 1. Assessment of tumor response was performed after every three treatment cycles, except in the case of clinically progressive disease or severe toxicity. Treatment was to be administered until disease progression, unacceptable toxicity, or consent withdrawal. Thereafter, continuation of treatment with CPT-11 was allowed on a compassionate basis, at the discretion of the investigator.

Atropine at a dose of 0.25 mg was administered s.c. at the occurrence of a cholinergic syndrome and in following cycles before CPT-11 infusion. No prophylactic treatment was permitted for diarrhea. Specific guidelines for curative treatment of delayed diarrhea were loperamide 2 mg every 2 h for 12 h after the last loose stool, and for a maximum of 48 consecutive hours. If diarrhea persisted for more than 24 h, an oral prophylactic broad-spectrum quinolone antibiotic was prescribed. If diarrhea persisted for more than 48 h, the patients were admitted to hospital for parenteral rehydration and another antidiarrheic treatment (i.e. octreotide). The patients with concomitant vomiting/fever or a PS >2 were subjected to i.v. rehydration.

Assessment of response

The primary efficacy endpoint assessed was the objective response rate. The response to treatment was classified according to WHO criteria [15]. When response or disease stabilization was observed, this was confirmed after a minimum interval of 4 weeks. Time to disease progression and overall survival were calculated from the start of the treatment.

All adverse events experienced during the study were recorded and graded according to the National Cancer Institute's (NCI) common toxicity criteria. All patients were evaluated for adverse events regardless of their relationship to the study drug. All adverse events were graded for severity before each treatment cycle.

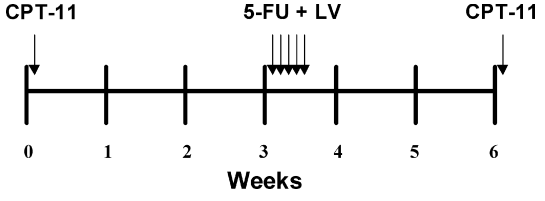

Fig. 1 Study treatment schedule

Table 1 Dose modification guidelines for toxicity

	At the time of i.v. infusion	At any time
Hematological toxicity		
Absolute neutrophil count	$<1.5\times10^9$/l	$\leq 0.5\times10^9$/l or $\leq 1.0\times10^9$/l plus fever/infection
Platelet count	$<75\times10^9$/l	$\leq 25\times10^9$/l
Non-hematological toxicity[a]		
Treatment-related diarrhea	Grade 2 or less	Grade 3/4
Mucositis	Grade 2 or less	Grade 3/4
Actions	Postpone i.v. infusion until ANC $\geq1.5\times10^9$/l, platelet count $\geq75\times10^9$/l, diarrhea not more than grade 0 and mucositis not more than grade 0	Postpone i.v. infusion until ANC $\geq1.5\times10^9$/l, platelet count $\geq75\times10^9$/l, diarrhea not more than grade 1 and mucositis not more than grade 1
Following doses	Complete dose	Reduction of dose: 5-FU 400 mg/m^2, CPT-11 300 or 250 mg/m^2

[a]At any time, other grade 3/4 toxicities were considered. After 2 weeks of delay, treatment had to be discontinued

Statistical methods

Prior studies showed percentages of objective response of CPT-11 alone or in combination with 5-FU/LV ranging from 15% to 32% [7, 8, 18, 22, 23]. A sample size of 43 patients was calculated assuming an expected objective response rate of 30%, a two-sided protection level against type I errors of 0.05 and a statistical power of 0.80.

The statistical analyses were performed using SAS software (SAS Institute, Cary, N.C). All patients were included for efficacy and toxicity analysis on an ''intention-to-treat'' basis. Kaplan-Meier estimations were used for the analysis of prognostic data and comparisons were made using a two-tailed log-rank test. The adverse events and response were calculated by punctual estimation with a 95% confidence interval (95% CI).

Results

Characteristics of patients

A total of 43 patients were enrolled at eight oncology departments in Spain. The patient and disease characteristics are listed in Table 2. The median time since primary tumor diagnosis was 5.5 months. Most of the patients (63%) had one metastatic site and one organ involved (74%). The most frequently affected organ was the liver (46%) followed by the lung (16%). Five patients (12%) and ten patients (23%) had been previously treated with radiotherapy (the irradiated target tumors were not considered for evaluation of response) and adjuvant chemotherapy, respectively. One patient had received palliative chemotherapy before study entry, and it was considered as a protocol deviation.

Table 2 Baseline patient and disease characteristics. Values are no. (%) of patients, except age in years

Number of patients	43
Sex	
Male	26 (60)
Female	17 (40)
Age (years)	
Median	57
Range	31–77
ECOG performance status	
0	27 (63)
1	16 (37)
Primary tumor location	
Colon	27 (63)
Rectum	16 (37)
Number of metastatic sites	
One	27 (63)
Two	14 (32)
Two	2 (5)
Location of metastases	
Liver	20 (46)
Lung	7 (16)

Drug exposure

A total of 179 cycles were administered during the study with a median of four per patient (range one to nine). CPT-11 dose was reduced in 14 cycles (8%) due to hematological toxicity (1 cycle), nonhematological toxicity (7 cycles), both (1 cycle), and non-drug-related causes in 5 cycles. Treatment with CPT-11 was delayed in 32 cycles (18%) due mainly to non-drug-related causes (18 cycles) and hematological toxicity (13 cycles). Moreover, 95% of the cycles were administered without reduction in the 5-FU dose and 5-FU administration was delayed in 16 cycles (9%), but only 3 cycles were delayed due to the lack of full recovery of CPT-11-induced hematological toxicity. The median relative dose intensity was 93% for both CPT-11 and 5-FU.

Safety

All patients were assessed for toxicity. The most frequent grade 3/4 adverse events relating to CPT-11 administration were late diarrhea, nausea and vomiting and neutropenia (Table 3). Grade 3/4 late diarrhea was observed in five cycles (2.8%) and four patients (9.3%), and grade 3/4 neutropenia was found in four cycles (2.2%) and three patients (7.0%). Only one patient experienced febrile neutropenia in one cycle. The most frequent grade 3/4 adverse events relating to 5-FU administration were neutropenia, mucositis, nausea and vomiting, and late diarrhea (Table 3). As expected, some

Table 3 Grade 3/4 toxicity (NCI-CTC) related to CPT-11 and 5-FU/LV

Adverse event	Related to CPT-11		Related to 5-FU/LV	
	Cycles ($n=179$) n (%)	Patients ($n=43$) n (%)	Cycles ($n=179$) n (%)	Patients ($n=43$) n (%)
Non-hematological				
Late diarrhea	5 (2.8)	4 (9.3)	2 (1.1)	2 (4.7)
Nausea	4 (2.2)	4 (9.3)	3 (1.7)	3 (7.0)
Vomiting	3 (1.7)	3 (7.0)	1 (0.6)	1 (2.3)
Mucositis	1 (0.6)	1 (2.3)	6 (3.4)	6 (14.0)
Hematological				
Neutropenia	4 (2.2)	3 (7.0)	13 (7.2)	7 (16.3)
Febrile neutropenia	1 (0.6)	1 (2.3)	1 (0.6)	1 (2.3)

Table 4 Overall response rate on intention-to-treat basis ($n=43$)

	Number	%
Complete response	4	9
Partial response	9	21
Stable disease	20	47
Progressive disease	10	23
Overall response rate (95% CI)	13	30 (16–44)

cases of grade 3/4 mucositis were found and grade 3/4 neutropenia was found in more cycles (13, 7.2%) and patients (7, 16.3%) than during CPT-11 administration.

Four patients were withdrawn from the study due to adverse events (diarrhea $n=1$, asthenia $n=1$, impaired PS $n=1$, gastric intolerance $n=1$), although there were no toxic deaths.

Efficacy

All patients were evaluated for efficacy on an intention-to-treat basis (Table 4). An objective response was seen in 13 patients (four complete responses and nine partial responses), with an overall response rate of 30% (95% CI 16–44). Stable disease was seen in 20 patients (47%), and 10 patients (23%) progressed.

Ten patients (23%) received prior adjuvant chemotherapy consisting of 5-FU or 5-FU/LV. The analysis of efficacy in these patients showed a similar overall response rate (30%; 95% CI 2–58) with three partial responses, five patients showing stable disease and two patients showing progression.

With a median follow up of 14.5 months, the median time to progression was 9.0 months (95% CI 6.2–12.0) and the median overall survival time was 18.5 months (95% CI 13.6–23.5). In 13 responding patients, the median duration of response was 8.9 months (95% CI 4.8–14.9). A Kaplan-Meier plot of overall survival is presented in Fig. 2.

Discussion

In the present multicenter phase II study, the efficacy and safety of an alternating combination of CPT-11 with 5-FU/LV were assessed in the treatment of metastatic CRC. The synergistic antitumor effect found in preclinical studies provided a basis for the clinical development of the CPT-11/5-FU combination [6, 10, 11, 17]. The combination of CPT-11 with 5-FU-based regimens using weekly schedules was initially evaluated in phase I studies performed in CRC patients [24, 30]. Antitumor response was not a primary objective of these dose-finding studies, but objective responses were found with a manageable toxicity. Several phase II studies have been performed in the United States and Europe with CPT-11 and 5-FU combined simultaneously, sequentially, or in an alternating fashion [10, 14]. In addition, two phase III studies have been reported with CPT-11 and 5-FU given simultaneously, and these have shown a significantly improved survival over 5-FU regimens alone [9, 25].

The antitumor efficacy and toxicity of the combination of CPT-11/5-FU has been found to be dose- and sequence-dependent [6]. In a phase I study performed in France the feasibility, safety profile and pharmacokinetic interaction of CPT-11 combined with 5-FU were evaluated [3]. CPT-11 given before 5-FU showed a minor pharmacokinetic interaction between both drugs, resulting in significantly lower 5-FU catabolism. This finding indicates that CPT-11 should be given before 5-FU, as done here. However, to our knowledge, only one study has been reported in which a similar schedule was used [29]. Table 5 summarizes the main findings of previous studies performed with an alternating schedule of CPT-11 and 5-FU with LV as biochemical modulator.

In our study, the alternating schedule reached an overall objective response of 30% whereas 47% of patients showed stable disease. These data are similar to those found by Van Cutsem et al. [29] who reported an overall response rate of 30% and stable disease in 49% of treated patients. In both studies, three-quarters of the patients benefited in terms of tumor growth control. Improved response rate and duration of response are still used as major endpoints of clinical trials in advanced CRC, but some studies have shown that stabilization of advanced CRC is associated with both prolonged survival and subjective improvement [27]. Preliminary results from a study using the same alternating schedule and of another using an alternating

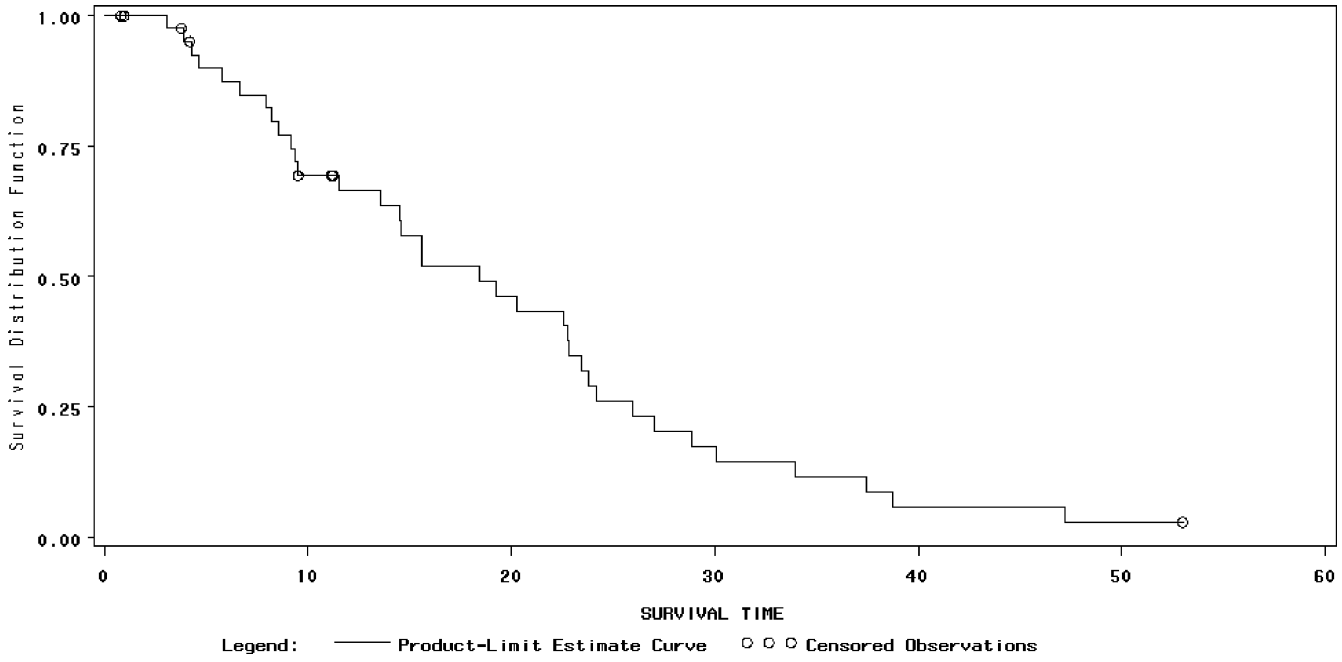

Fig. 2 Overall survival

Table 5 Clinical trials using the alternating schedule of CPT-11 and 5-FU/biochemical modulator in first-line chemotherapy of metastatic colorectal cancer patients (*CR* complete response, *MR* minor response, *PR* partial response, *DNR* data not reported)

Reference	N	Schedule	Response	Survival (months)
2[a]	33	CPT-11 350 mg/m^2 90 min i.v. infusion every 6 weeks; 5-FU 425 mg/m^2 i.v. bolus five consecutive days (days 22–26); LV 20 mg/m^2	13.7% MR, 31.0% PR	DNR
21[a]	71	CPT-11 100 mg/m^2 90 min i.v. infusion each week for 4 weeks plus 2-week rest period; 5-FU 425 mg/m^2 i.v. bolus five consecutive days (days 1–5) every 4 weeks; LV 20 mg/m^2	32% CR/PR	17.6
29	33	CPT-11 350 mg/m^2 90 min i.v. infusion every 6 weeks; 5-FU 425 mg/m^2 i.v. 15-min infusion five consecutive days (day 22–26); LV 20 mg/m^2	3% CR, 27.3% PR	16
Present study	43	CPT-11 350 mg/m^2 90 min i.v. infusion every 6 weeks; 5-FU 425 mg/m^2 i.v. bolus five consecutive days (day 22–26); LV 20 mg/m^2	9% CR, 21% PR	18.5

[a]Preliminary results

schedule with different CPT-11 or 5-FU doses have also shown significant objective response rates: 44.7% including 13.7% minor responses [2] and 32% [21]. We did not find any differences in the response rate compared to those patients previously treated with 5-FU or 5-FU/LV in the adjuvant setting.

A median progression-free survival of 9.0 months and a median survival of 18.5 months supported the clinical value of the response rate found here. Again, these data confirm those found by Van Cutsem et al. [29]: 7.2 and 16 months, respectively. Other alternating schedules have shown values of 6.9 and 17.6 months [21]. These results on efficacy compare favorably with the response rate of 23% and the median survival of 12 months found in first-line chemotherapy using single-agent 5-FU/LV [1] and with the response rate of 15–32% and the median survival of approximately 12 months using single-agent CPT-11 [7, 8, 18, 23]. The efficacy of this alternating schedule, which is higher than that of either single agent, seems to confirm the additive effect of the two drugs found in previous studies [29].

The theoretical risk of the CPT-11/5-FU/LV combination is related to their partially overlapping toxicity profile, and hence an increase in side effects, which would lead to dose reduction because the main dose-limiting toxicities of both drugs are neutropenia and diarrhea. Nevertheless, the alternating schedule used here allowed the administration of the originally planned dose in more than 90% of all cycles, and no meaningful differences were found between CPT-11 (92%) and 5-FU/LV (95%) regarding the need for dose modification in the cycles. Moreover, the incidence of grade 3/4 toxicity was low, and no treatment-related death was documented. In fact, dose reduction has been more frequent in studies using simultaneous or sequential schedules of CPT-11/5FU/calcium folinate [9]. These results indicate the feasibility of this alternating program

and confirm previous studies of alternating CPT-11 and 5-FU schedules using LV as biochemical modulator [2, 21, 29]. Apart from alopecia, the main drug-related toxicities were diarrhea and neutropenia. Grade 3/4 late diarrhea was mainly related to CPT-11 rather than to 5-FU (9.3% vs 4.7% of patients) whereas grade 3/4 neutropenia was more frequent after 5-FU administration (16.3% vs 7.0% of patients). No differences were found in the incidence of grade 3/4 febrile neutropenia. The incidence of severe mucositis was higher after 5-FU administration (14.0% vs 2.3% of patients). Nevertheless, the overall incidence of severe diarrhea or neutropenia is similar or even lower than that reported in previous studies using the alternating schedule [21, 29]. Moreover, the toxicity pattern found with the alternating schedule was similar to that reported in studies using 5-FU/LV [4] or CPT-11 first-line monotherapy [20].

In conclusion, we found that the alternating combination of CPT-11 350 mg/m^2 and 5 days bolus of 425 mg/m^2 5-FU and low-dose (20 mg/m^2) LV showed a good tolerability and clinical response. The present trial, as well as other previous studies [2, 21, 29], indicate that the alternating regimen of CPT-11 and 5-FU modulated with LV should be considered as an option in the first-line treatment of patients with metastatic CRC. Further phase III trials comparing the alternating versus the concomitant administration of CPT-11 and 5-FU/LV are required to support this evidence.

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