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REVIEW ARTICLE

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Treatment of patients with peritoneal metastases from gastric cancer

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Abstract

Despite recent advances in chemotherapy, outcomes of patients with peritoneal metastases (PM) from gastric cancer are still very poor and standard treatment has not been established. Although oral S-1 appears to be effective for patients with PM, the effects of systemic chemotherapy are limited. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) yield fewer benefits in patients with PM from gastric cancer than in patients with PM from other malignancies. In comparison, repeated intraperitoneal chemotherapy (RIPEC) with taxanes using an implantable peritoneal access port has a pharmacokinetic advantage for the control of peritoneal lesions and in combination with systemic chemotherapy can result in surprisingly long-term survival in patients with PM from gastric cancer. Herein, we review the results of recent clinical studies specifically targeting PM from gastric cancer and discuss future prospects for an intraperitoneal approach to the ideal treatment of patients with gastric cancer with peritoneal involvement.

KEYWORDS
gastric cancer, HIPEC, intraperitoneal chemotherapy, peritoneal metastasis

1 | INTRODUCTION

Gastric cancer is the fifth most common malignancy worldwide, and the third leading cause of cancer-related deaths.[1] The peritoneum is the most frequent site of metastases and recurrences in patients with gastric cancer.[2,3] Although various approaches have been attempted such as extended resections, combination chemotherapy, heated intraperitoneal chemotherapy and immunotherapy, the prognosis of patients with peritoneal metastases (PM) is still very poor and there is no established standard treatment.

In general, these patients are treated with systemic chemotherapy similar to patients with other distant metastases. Based on the results of Asian phase III trials,[4,5] fluoropyrimidine plus platinum agents are considered to be the standard regimens for advanced or recurrent gastric cancer, although docetaxel or anthracyclines are combined to treat patients in Western countries.[6,7] However, the efficacy of these regimens for patients with PM is still unclear. Patients with PM with massive ascites are often excluded from clinical trials because of their poor general condition. Although the survival of patients with PM is supposed to be worse compared to patients without PM from gastric cancer who received chemotherapy,[8] there are few clinical trials specifically targeting patients with PM, probably because of the lack of measurable disease.

Intraperitoneal (IP) infusion of anticancer drugs was intended to enable an increased dose and time of exposure of intra-abdominal tumor cells to anticancer drugs with minimal systemic toxic effects. In fact, IP administration has been shown to result in a higher drug concentration and longer half-life in the peritoneal cavity compared

with intravenous administration, although this is affected by a variety of biophysical parameters, including molecular weight, charge and solubility.[9,10] Hyperthermia has been shown to increase the beneficial effects of anticancer agents by augmenting cytotoxicity and/or increasing the penetration of the drugs into tissue.[11] Based on this theoretical background, hyperthermic intraperitoneal chemotherapy (HIPEC) combined with cytoreductive surgery (CRS) have been used mainly in Western countries as a general treatment for PM from various malignancies.

Recently, repeated intraperitoneal chemotherapy (IPC) has been used, administered with a subcutaneous infusion port connected to an intraperitoneal catheter. Once the port is implanted, anticancer drugs can be repeatedly injected into the abdominal cavity without additional surgical stress. This method has been most vigorously evaluated in patients with ovarian cancer and, based on the results of phase III studies,[12,13] repeated IPC is now recommended for patients with Stage III epithelial ovarian cancer after optimal debulking surgery according to the National Comprehensive Cancer Network Guideline.[14] In this review, we summarize current clinical data on the multidisciplinary treatment of this disease, mainly focused on repeated IPC and then refer to recent developments in drug modification and delivery systems which may achieve better clinical results for patients with PM from gastric cancer.

2 | SYSTEMIC CHEMOTHERAPY

Although previous phase III trials have established standard systemic therapy regimens for patients with metastatic gastric cancer, some anticancer drugs such as cisplatin or irinotecan, cannot be safely given to patients with PM, because of severe and sustained toxicity causing intestinal stenosis or ascites. Therefore, until recently, large-scale trials have not been conducted for patients with PM and a standard chemotherapy regimen for these patients has yet to be established.

Table 1 shows the results of recent studies (within 10 years) of systemic chemotherapy targeted specifically for patients with PM from gastric cancer. Historically, 5-fluorouracil (5-FU) has been used as the key drug for patients with PM, and many regimens using other drugs combined with 5-FU have been evaluated. Median survival time (MST) of patients in these studies was 8.0~13.2 months.[15-19] Paclitaxel (PTX), which is generally used as second-line treatment for patients with metastatic gastric cancer, was expected to be effective for PM because of favorable pharmacokinetics.[20,21] However, the effects of systemic PTX alone seems to be limited for patients with PM.[17,22] Recently, nanoparticle albumin-bound paclitaxel (Nab-PTX) has been shown to elicit a higher antitumor effect in a peritoneal xenograft model[23] and used for clinical trials, although the results are still premature.[24]

S-1 is an oral fluoropyrimidine derivative, combining tegafur with two modulators, and is considered to be a pivotal agent for the treatment of patients with gastric cancer in Japan. Small-scale studies, with notable efficacy for S-1 alone[25] or in combination with cisplatin[26] or docetaxel[27] have been reported, suggesting superior results for S-1 in the control of PM compared with other 5-FU derivatives. Taken together, however, these results suggest that the effects of systemic administration are considered to be limited presumably as a result of the so-called "peritoneal-plasma barrier" which prevents effective drug delivery from the systemic circulation to peritoneal lesions.

3 | CYTOREDUCTIVE SURGERY AND HIPEC

Hyperthermic intraperitoneal chemotherapy combined with total peritonectomy was originally developed by Sugarbaker based on the concept that peritoneal metastasis is a localized disease in the abdominal cavity.[28] At specialized centers in Western countries, this

TABLE 1 Clinical outcomes of systemic chemotherapy for gastric cancer with PM

Author, Year	Regimen	Study	n	MST (mo)	1y-OS (%)	RR (%)
Imazawa, 2009[15]	5Fu + MTX	P2	31	9	16	25
Oh, 2007[16]	FOLFOX-4	P2	48	8.4	27	33
Iwasa, 2012[17]	5Fu + leukovorin + PTX	P1/2	25	8.0	–	–
Shirao, 2013[18]	5Fu + MTX 5Fu continuous infusion	P3	103 102	10.6, 9.4	40.7, 37	–
Masuishi, 2017[19]	FOLFOX-4	R/S	10	13.2	–	
Imamoto, 2011 [22]	PTX	R/S	64	5.2	–	39
Ishizone, 2006[25]	S-1	P2	16	18	–	
Shitara, 2013[26]	(S1/Cap) + CDDP	R/S	120	15.9	60<	–
Shigeyasu, 2013[27]	S1 + docetaxel	P2	19	15.3	58	–
Shitara, 2017[24]	PTX	P3	248	10.9	–	–
	Nab-PTX (triweekly)		247	10.3		
	Nab-PTX (weekly)		246	11.1		

Cap, capecitabine; CDDP, cisplatin; FOLFOX-4, oxaliplatin, leucovorin and 5-fluorouracil; 5Fu, 5-fluorouracil; MST, median survival time; MTX, methotrexate; Nab-PTX, nanoparticle albumin-bound paclitaxel; OS, overall survival; PM, peritoneal metastases; PTX, paclitaxel; P1, P2, P3; phase I, II, III; R/S, retrospective study; -, not described.

aggressive approach has been carried out mainly in patients with pseudomyxoma, mesothelioma, ovarian and colorectal cancers, which suggested considerable efficacy for PM as a result of these malignancies. However, evidence for this strategy against PM from gastric cancer is relatively scarce because of the low frequency of this condition in Western countries. In Asia, HIPEC combined with modified surgery has been used to treat patients with gastric cancer in specialized centers for many years, but large-scale comparative studies have not been done, probably because of the high toxicity associated with these regimens.

Table 2 summarizes recent reports on cytoreductive surgery (CRS) and HIPEC in the treatment of patients with PM from gastric cancer including two phase III studies. As in ovarian and colorectal cancer, mitomycin (MMC), cisplatin (CDDP) and, more recently, oxaliplatin, have been used for HIPEC.[29-34] However, MST of the patients was 9.2~11.5 months and the 1-year survival did not exceed 50%, except in a small-scale phase II study that shows a MST of 19 months in patients treated with HIPEC followed by systemic treatment with FLOT (5Fu + leukovorin + oxaliplatin + docetaxel) regimen.[35] Even in patients who received optimal cytoreduction, MST remains at 15~25 months, which is significantly worse than the survival of patients with ovarian cancer or colorectal cancer and does not exceed the survival in patients treated with systemic chemotherapy.

The lack of appreciable increase in survival is presumably caused by a higher malignant potential of disseminated gastric cancer cells. Moreover, morbidity was 14.7%~88% with significant mortality. Although other drug combinations may improve outcomes, it is suggested that HIPEC results in less benefit for patients with PM from gastric cancer compared with patients with PM from other malignancies. A recent review suggests this aggressive treatment should be used only in patients with a low peritoneal carcinoma index (PCI <6) and a good response with negative cytology after HIPEC in patients with gastric cancer.[36]

4 | REPEATED INTRAPERITONEAL CHEMOTHERAPY USING TAXANES

The most significant shortcoming of HIPEC is that a single dose, even with hyperthermia, is not sufficient to allow the anticancer drugs to infiltrate into the deep portion of metastatic lesions on the peritoneal surfaces, and therefore multiple IP doses are needed to result in marked antitumor effects on the PM. Repeat IP infusion of anticancer drugs using an implantable port system was carried out over a decade ago. To treat patients with PM from gastric cancer, neoadjuvant MMC and CDDP were used. However, the clinical effects of those series were disappointing, probably because those drugs are readily absorbed into the systemic circulation and do not stay in the abdominal cavity for a long time. Indeed, pharmacokinetic studies have shown relatively low ratios using area under the curve analysis comparing peritoneal cavity levels to the systemic compartment after IP doasage of MMC or CDDP.[10,37] Therefore, this approach has long been abandoned in clinical trials.

In this century, however, attention is again focused on repeated intraperitoneal chemotherapy (RIPEC) using taxanes (Figure 1). Taxanes such as PTX and docetaxel (DTX) are insoluble in water and solubilized with a specific agent, Cremophor EL, and ethanol (Taxol®, BMS, New York, USA) or polysorbate 80 (Taxotare®, Sanofi, Paris, France), respectively. These form relatively large particles (10-12 nm in diameter) in solution and are gradually absorbed through the lymphatic system only, which results in prolonged retention in the peritoneal cavity.[38,39] After IP infusion, taxanes show much higher area under the curve ratios than other hydrophilic drugs when comparing levels in the peritoneum to the plasma.[10,40] Even if they are infused many times, taxanes rarely result in peritoneal adhesions which may prevent drug diffusion to PM, probably because of their strong antiproliferative effects. These two biological characteristics are a major advantage for RIPEC.

Based on these basic findings, RIPEC using PTX or DTX at normothermic conditions has been attempted for the treatment of patients with PM from gastric cancer mainly in Japan. In those studies, IP taxanes were combined with systemic chemotherapy as neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) and the results were already summarized in a previous review.[41] As shown in Table 3, this approach resulted in a MST of 15.1~24.6 months and 1-year survival of over 70%,[42-49] which are considerably better than results with systemic chemotherapy or HIPEC.

In fact, second-look laparoscopy showed a drastic macroscopic change in the appearance of PM in many patients (Figure 2). The

TABLE 2 Clinical outcomes of CRS and HIPEC for gastric cancer with PM

Author, Year	Regimen	Study	n	MST (mo)	Survival (%)	Morbidity % (Mortality %)
Hall, 2004[29]	MMC	P2	34	11.2	1 y OS, 45 (CC0/1) 16 (CC2)	35 (–)
Yonemura, 2005[30]	MMC + CDDP	R/S	107	11.5	5 y OS, 6.7	21.5 (2.8)
Glehen, 2010[31]	MMC + CDDP or L-OHP + CPT-11	R/S	159	9.2	1 y OS, 43 (CC0; 65)	27.8 (6.7)
Yang, 2011[32]	MMC + CDDP	P3	34	11.0	1 y OS, 41	14.7 (–)
Magge, 2014[33]	MMC + CDDP	P2	23	9.5	1 y OS, 50	52.2 (4.3)
Muller, 2014[35]	L-OHP + DTX	P2	26	19	2 y OS, 38	23 (0)
Rudloff, 2014[34]	L-OHP	P3	9	11.3	1 y OS, 44	88 (11)

CDDP, cisplatin; CPT-11, irinotecan; CRS, cytoreductive surgery; DTX, docetaxel; 5Fu, 5-fluorouracil; HIPEC, hypothermic intraperitoneal chemotherapy; L-OHP, oxaliplatin; MMC, mitomycin; MST, median survival time; OS, overall survival; PM, peritoneal metastases; P2, P3, phase II, phase III; R/S, retrospective study; CC-0, CC-1, complete resection-0, -1;-, not described.

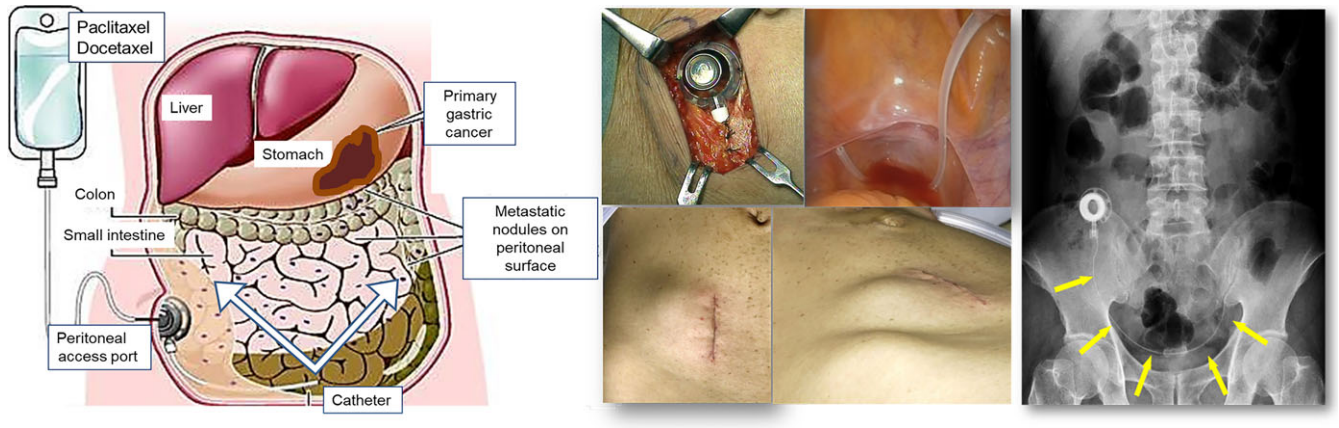

FIGURE 1 Left: Repeated intraperitoneal chemotherapy using an implantable port system. The catheter is placed in the pouch of Douglas (arrows) and taxanes dissolved in 500~1000 mL saline infused over 60 min. Right: Representative laparoscopic and X-ray views of intraperitoneal port and catheter

TABLE 3 Clinical outcomes of repeated IPC with systemic chemotherapy for gastric cancer with PM

Author, Year	IP regimen	Systemic regimen	Study	n	MST (mo)	1 y OS (%)	Cytology negative conversion rate (%)
Ishigami, 2010[42]	PTX (20 mg/m^2)	S-1 + PTX	P2	40	22.5	78	86
Fujiwara, 2012[43]	DTX (40~60 mg/m^2)	S-1	R/S	18	24.6	76	78
Fushida, 2013[44]	DTX (45 mg/m^2)	S-1	P1/2	39	16.2	70.4	81
Yamaguchi, 2013[45]	PTX (20 mg/m^2)	S-1 + PTX	P1	35	17.6	77.1	97
Ishigami, 2016[46]	PTX (20 mg/m^2)	S-1 + PTX	P3	114	17.7	71.9	95
Fujiwara, 2016[47]	PTX (40 mg/m^2)	S-1 + L-OHP	P2	60	NR	71.5	71
Fukushima, 2017[48]	DTX (10 mg/m^2)	Cap + CDDP	P2	48	NR	75	76
Cho, 2017[49]	DTX (100 mg/m^2)	Cap + CDDP	P1/2	39	15.1	–	–

Cap, capecitabine; CDDP, cisplatin; DTX, docetaxel; IPC, intraperitoneal chemotherapy; L-OHP, oxaliplatin; MST, median survival time; NR, not reached; OS, overall survival; PM, peritoneal metastases; PTX, paclitaxel. P1, 2, 3, phase I, II, III; R/S, retrospective study; -, not described.

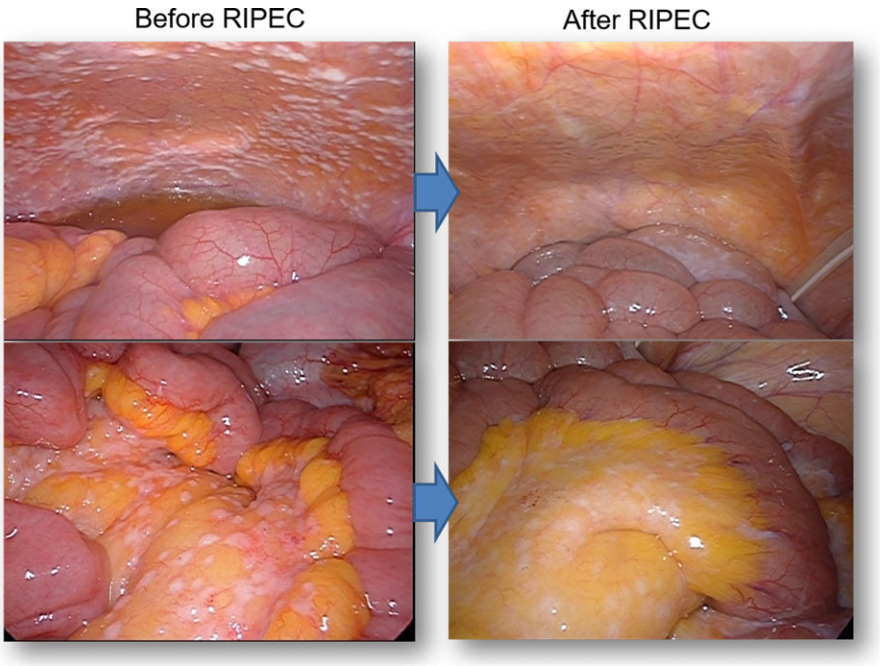

FIGURE 2 Representative laparoscopic views of peritoneal metastases before and after repeated intraperitoneal chemotherapy

mechanism for marked shrinkage of peritoneal tumors has not been fully elucidated. However, murine studies have shown that PTX, given as a single IP infusion, directly infiltrates up to several hundred micrometers beneath the surface of peritoneal nodules and induces massive destruction of tumor cells as well as microvessels in the tumor periphery.[50,51] Thus, repeated doses of IP PTX might eradicate deeper tumor cells. Drastic changes in the peripheral structure of each nodule may reduce intratumor pressure and enhance the delivery efficiency of systemically infused anticancer drugs, which might be another important mechanism to explain the remarkable antitumor effects against PM. If gastrectomy is carried out in patients with a good response, MST reached 26.5~30.5 months.[52,53] Determining the appropriate criteria and timing for conversion surgery is an important clinical subject for the future.

Another important advantage of RIPEC is relatively mild toxicity compared with HIPEC. According to one series, grade 3/4 neutropenia occurred in 21%~50%[42,45-48] and port-related complications such as infection, occlusion and reflux occurred in 20.6%.[54] However, non-hematological toxicities were relatively rare with no treatment-related deaths. It is notable that abdominal pain, which is often considered to be a dose-limiting toxicity in IPC, was rarely observed probably because of the low dose of IP taxanes.

Patients with only isolated tumor cells in the peritoneal cavity (P0CY1) also have dismal long-term outcomes and there is no established consensus to direct treatment.[55] As this strategy can cause remarkable shrinkage of macroscopic tumors, RIPEC can be expected to be more effective against P0CY1 cases. In fact, the cytology converted to be negative in 71%~97% of patients with PM,[42-48] which has never been achieved in other methods in previous reports. Moreover, when used for P0CY1 cases, 1-year OS rate was 84.2% with negative change of cytology in 94.7% patients.[56] This suggests that RIPEC with taxanes has the splendid power to control peritoneal micrometastases and thus may be a promising strategy for the prevention of peritoneal recurrence for gastric cancer with serosal exposure.[57]

As pharmaceutical companies are not interested in clinical trials of drugs with an already expired patent, a reasonable drug-approval system needs to be established for the sake of patients with this dismal condition.

5 | OTHER NOVEL INTRAPERITONEAL TREATMENTS

Catumaxomab is a trifunctional monoclonal antibody with two different antigen-binding sites, EpCAM, CD3 and a functional Fc domain, thereby activating a complex antitumor immune reaction.[58] Heiss et al reported that IP injection of catumaxomab improved puncture-free survival and had a better trend in survival in patients with malignant ascites.[59] Based on these results, catumaxomab has been licensed for clinical use in the European Union since 2009 for patients with malignant effusions. Goere et al have shown clinical efficacy for the treatment of patients with PM from gastric cancer.[60]

Bevacizumab, a humanized variant of an antivascular endothelial growth factor (VEGF) antibody, might be another useful drug for the treatment of malignant ascites.[61] Fushida et al have shown that systemic infusion of anti-VEGF antibody is effective in patients with malignant ascites.[62] More recently, the effectiveness of immune checkpoint blocking antibodies has been reported in patients with metastatic gastric cancer.[63] Although no clinical trials are targeted for patients with PM from gastric cancer, the use of these antibody preparations with IPC might be promising.

Nanodrugs, a new drug formulation, measuring 20-100 nm in molecular diameter are another promising approach for patients with PM. Nanodrugs are preferentially accumulated in tumor tissue as a result of the enhanced permeability and retention (EPR) effect.[64] PMB-30W is a water-soluble, amphiphilic polymer composed of 2-methacryloxyethyl phosphorylcholine and n-butyl methacrylate and enables the construction of PTX-containing nanoparticles.[65] IP administration of PTX formulated with PMB-30W resulted in deeper penetration into peritoneal nodules and showed enhanced antitumor effects against peritoneal xenografts of human gastric cancer compared with conventional cremophor-conjugated PTX in murine models.[50,66] In the same model, the intraperitoneal administration of another PTX-incorporating polymeric micellar nanoparticle, NK105, was shown to have significantly greater antitumor effects compared with IP Taxol®.[67] As NK105 was already used as a second-line treatment for patients with recurrent gastric cancer with an excellent response,[68] IP chemotherapy with NK105 might be useful for clinical trial.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel technique which delivers anticancer drugs into the closed abdominal cavity as an aerosol under pressure.[69] This unique drug delivery technique is based on the concept that generating an artificial pressure gradient with a laparoscopic procedure can enhance tissue uptake with homogeneous distribution of vaporized drugs within the closed abdominal cavity. According to a recent report by Nadiradze et al, 24 patients with PM from gastric cancer treated with PIPAC using low-dose cisplatin and doxorubicin had a MST of 15.4 months.[70] Although these are early results, this method may be another promising strategy for the treatment of PM.

Cell-free and concentrated ascites reinfusion therapy (CART) was originally developed for patients with cirrhotic ascites, but is fairly effective for palliation in patients with massive ascites. After recent technological improvements, autologous ascites which contains a large number of proteins and nutrients, can be reinfused without severe toxicity, often resulting in a drastic improvement of the general condition of cachectic patients with PM.[71,72] In fact, induction of CART enables patients with highly advanced PM and massive ascites to receive IPC with improved survival.[73]

6 | CONCLUSION

For many years, PM from gastric cancer have been considered a terminal condition, and treatment has typically been palliative. Repeated

IPC with taxanes enables delivery of a high concentration of drugs to the tumor cells in the peritoneal nodules, and seems to be the best approach for the treatment of PM so far. However, the effectiveness of IPC critically depends on how homogeneously the drug can be distributed in the entire abdomen and how deeply the drug can infiltrate into the peritoneal tumors. Many factors are related to the distance of drug penetration in solid tumors and the mechanisms are still largely unknown.[74] Drug modification as well as improved delivery systems to enhance drug infiltration in peritoneal tumors should further prolong the survival of these patients. The era is coming when PM of gastric cancer are manageable.

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