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Intratumoural administration of cisplatin in slow-release devices

I. Tumour response and toxicity

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Summary. In this study we investigated the effect of the incorporation of cisplatin in slow-release systems on tumour response and animal toxicity after intratumoural (i.t.) administration. Solid slow-release rods with incorporated cisplatin were prepared either from starch or from three different polyether-hydrogel formulations. In vitro release rates from these rods were widely different. With the starch system, approximately 100% release was obtained in 2 h. For the hydrogel formulations, release was approximately 100% in 1 day for a formulation with 40% water uptake (T3), 45% within 4 days for a formulation with 14% water uptake (T2) and 8% within 4 days for a formulation with 4% water uptake (T1). The slow-release rods containing graded amounts of cisplatin were implanted i.t. in s.c. RIF1 murine tumours. The i.t. administration of cisplatin in starch rods did not reduce animal toxicity or increase tumour response relative to i.t. injections of cisplatin in solution. For the hydrogel rods, the tumour response and animal toxicity for a given dose of cisplatin decreased with decreasing release rate. Higher doses of cisplatin could therefore be delivered with the slower-releasing hydrogel formulations. The slowest-release hydrogel rods (T1) had very little effect on either tumour (growth delay) or host (animal weight loss), even at cisplatin doses 8 times that tolerated as an i.p. injection. The fast (T3)- and intermediate (T2)-release hydrogel rods resulted in dose dependent tumour growth delays that were longer than those obtained with i.p. or i.t. administration of cisplatin. The highest response, a tumour growth delay of 55 days, was obtained with the intermediate-release hydrogel rods (T2) at a cisplatin dose of 40 mg/kg. Analysis of tumour growth delay for a given level of toxicity indicated that the intermediate-release formulation (T2) was slightly better than the fast-release formulation (T3) and confirmed the therapeutic advantage of i.t. implants over systemic therapy.

Introduction

Locoregional administration of currently available anticancer agents has been described as being a promising way to enhance their therapeutic efficacy [13]. The most direct way to achieve this is by intratumoural (i.t.) injection, which has been tried using a number of chemotherapeutic agents, with varying degrees of success [1, 5, 9, 20, 21, 23, 24, 27, 28]. High tumour concentrations can be achieved, whereas exposure of normal tissues is reduced [7, 22, 31]. Our group has been particularly interested in the application of the widely used chemotherapeutic agent cisplatin [*cis*-diamminedichloroplatinum(II)], which is also known to have radiosensitizing properties [7, 11, 26]. The ultimate aim of these studies was to maximize the therapeutic gain for the combination of cisplatin and irradiation by maintaining adequately high tumour concentrations throughout a radiotherapy course of several weeks.

A number of slow-release devices have been reported to release cisplatin over such long periods, including implants [14, 16], microspheres [25] and microcapsules [15]. Although in vivo release over a number of weeks has been demonstrated with these formulations, tumour response data after i.t. administration are limited. In a previous report we demonstrated that i.t. administration of cisplatin, with or without a collagen-matrix release system, resulted in an increase in tumour growth delay and a decrease in toxicity as compared with i.p. administration [8]. The collagen matrix proved to be a release system that showed full release within hours, which was too fast for our eventual goal. We therefore tested two other release vehicles, a starch-based system and a polymer-hydrogel system. Using the latter, we found that cisplatin release rates could be varied from hours to weeks. We report our studies using these systems to investigate the relationship between release rate and biological response, both for the tumour and for host toxicity.

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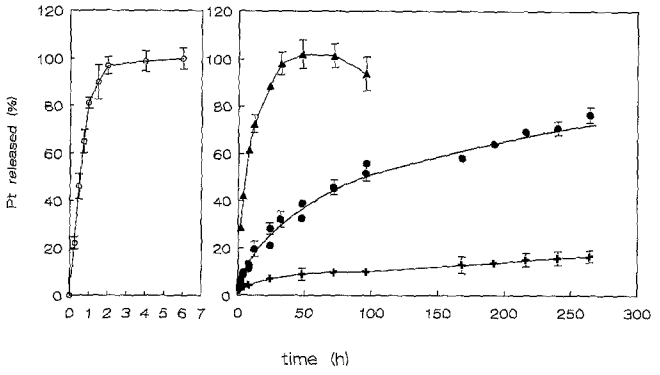

Fig. 1. In vitro release of Pt from cisplatin-starch rods (*left panel*) and hydrogel rods with different water uptakes (*right panel*) (mean ± SD; $n = 3$). The starch rods (○) contained 9.27% (w/w) cisplatin. Water uptakes were 4%, 14% and 40% (w/w) for T1 (+), T2 (●) and T3 (▲), respectively; the hydrogels contained 10% (w/w) cisplatin

Materials and methods

Slow-release formulations. Cisplatin was obtained from Ventron (Karlsruhe, FRG) as a crystalline powder and was incorporated in slow-release devices based either on starch (collaboration with the University of Groningen) or on a new type of hydrogel made from polyether polymers (collaboration with TNO, Delft). Both slow-release systems were prepared as solid rods. The starch rods were prepared by direct compression of a powder mixture containing 9.27% cisplatin by weight. Rods with diameters of 1.2 mm and lengths of 2.3–4.6 mm were prepared that had volumes of 2.6–5.2 µl and weights of 3.9–7.9 mg. Different doses of cisplatin were obtained by varying the length or number of starch rods to be implanted. For the polyether-hydrogel rods, three formulations with different water uptakes were studied, i.e. 4% (w/w) for formulation T1, 14% for T2 and 40% for T3. The hydrogels were prepared as rods with a diameter of 1.5 mm that were cut to a length of 5 mm, having a volume of 8.8 µl and a weight of 12–13 mg. Different doses of cisplatin were obtained by varying the payload of the cisplatin-containing hydrogels. Rods were prepared with payloads of 2%–17%, equivalent to cisplatin doses of 18–88 mg/kg for a 25-g mouse.

In vitro release. In vitro release of cisplatin from the slow-release devices was studied at 37° C in flat-bottomed vials on a shaker. The release medium consisted of phosphate-buffered saline (0.01 M; pH 7.4). Concentrations of cisplatin in the release medium were always <10% of the maximal solubility of cisplatin (sink conditions). Samples were taken at regular intervals and then analyzed for platinum (Pt) concentration using flameless atomic absorption spectrometry (FAAS) according to the method described previously [19].

Animals. Female C3H/Km mice, 8–12 weeks old and weighing 25–35 g, were used throughout the studies. The mice were obtained from the animal department of the Netherlands Cancer Institute and were bred under specific pathogen-free (SPF) conditions. The animals were kept on a 12-h light/12-h dark schedule and were fed standard mice chow and tap water ad libitum.

Tumour model. The RIF1 murine fibrosarcoma grown s.c. on the lower back was used in all in vivo experiments. The tumour was maintained by the protocol described by Twentyman et al. [29]. Tumours were obtained by s.c. inoculation of 2×10^4 cells in a volume of 0.1 ml. The mice were treated when the tumour reached a mean diameter of 8 ± 0.5 mm.

Drug administration. Solutions of cisplatin in saline were injected i.p. and i.t. The cisplatin solutions were freshly prepared on each day. Injection volumes were 0.01 ml/g body weight for the i.p. route and 0.1 ml/tumour for the i.t. route. Prior to i.t. drug administration, the mice were lightly anesthetized with an enflurane-oxygen mixture. The hair over the tumours was shaved and the tumours were disinfected with 70% ethanol. Cisplatin in solution was given i.t. by a single injection in the centre of the tumour. The slow-release rods were implanted in the tumour into small holes made using a 21-gauge needle. With the starch rods, one rod measuring 2.3, 3.5 or 4.6 mm in length was implanted in the centre of the tumour to give a dose of 12, 18 or 24 mg/kg, respectively; for doses of 30 and 36 mg/kg two rods were implanted parallel to each other. With the hydrogel rods, one rod measuring 5 mm in length was implanted in the centre of the tumour. The hydrogel rods used in the in vivo experiments had payloads that were equivalent to cisplatin doses of 10–88 mg/kg. The implant procedure was simple and quick to carry out. Little bleeding occurred and the rods remained in position for the duration of the experiment.

Tumour response and toxicity. Starting on the day of treatment, three perpendicular diameters of each tumour were measured with calipers until the tumour exceeded a mean diameter of 13 mm, at which time the mouse was killed. Tumour growth delay was assessed as being the time required for the tumour to reach 2 mm above the treatment diameter, corrected for the growth time of controls. Each mouse was also weighed 2–3 times/week until they had to be killed because of tumour burden. The percentage of change in weight from pretreatment values was calculated on each day and the maximal weight loss was determined for each mouse; this was then averaged for each treatment group.

Results

In vitro release of cisplatin

The starch rods swelled to approximately 3 times their initial diameter and length within 4 h after they had been placed in the aqueous release medium. Swelling of the hydrogel rods was less evident, although the water uptake of the polymer matrix was 4%, 14% and 40% (w/w) for T1, T2 and T3 rods, respectively. Widely different in vitro release rates, as measured from total platinum in the medium, were obtained for the different slow-release formulations (Fig. 1). Release of cisplatin was also evident from the color of the slow-release rods, which faded from yellow to transparent as the release progressed. All release profiles showed decreasing release rates with time (Fig. 1).

Release of platinum from the starch rods was rather fast, amounting to almost 100% within 2 h (Fig. 1, left panel). For the three hydrogel preparations with a 10% payload (Fig. 1, right panel), release rates ranged from 89% in 1 day and 100% in 2 days for the formulation with the greatest water uptake (T3) to 10% in 4 days and 17% in 11 days for the rods with the lowest water uptake (T1). The hydrogel rods with a 10% payload and intermediate water uptake (T2) released 56% of the incorporated Pt in 4 days and 75% in 11 days.

The effect of a change in payload on the release rate was studied for T2 hydrogel rods. The absolute amount of Pt released from the T2 hydrogel rods increased with increasing payloads (Fig. 2, top panel). Cumulative fractional release from these hydrogel rods, however, was dependent on the initial payload of the systems, decreasing with increasing payload (Fig. 2, lower panel). This is in accordance with equations developed for release from diffusion-controlled monolithic devices [3], which were found to adequately describe the in vitro release curves from these rods (data not shown).

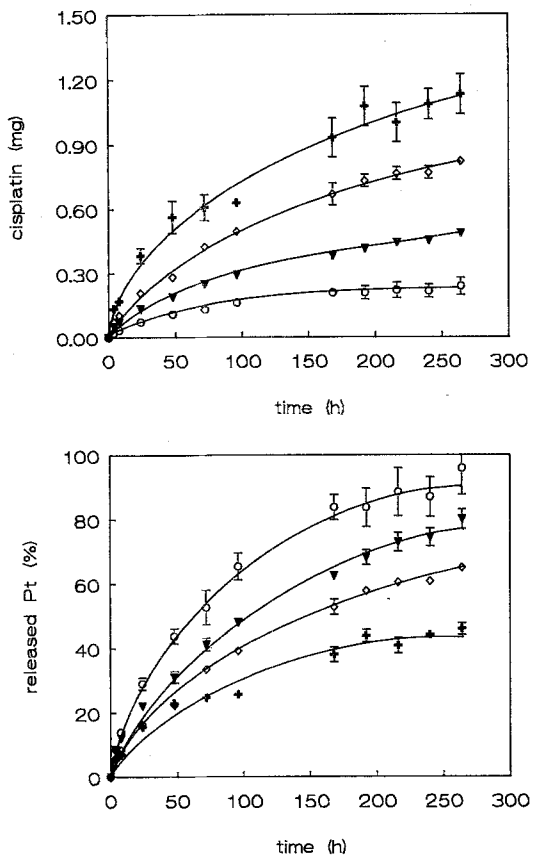

Fig. 2. Effect of payload on the in vitro release of Pt from cisplatin-hydrogel rods with 14% water uptake (mean ± SD; $n = 3$). Payloads were 1.9% (○), 4.7% (▼), 9% (◇) and 16.7% (+) (w/w). *Top panel*, cumulative release; *lower panel*, cumulative fractional release

Table 1. Maximum tolerated doses after administration of cisplatin solution by i.p. and i.t. injection and by i.t. implantation of cisplatin in slow-release rods

Treatment	Maximum tolerated dose (mg/kg)
Injection, i.p.	10
Injection, i.t.	20
Starch rods	17–24
Hydrogel rods:	
T1[a]	>80
T2	40–60
T3	30–40

[a] T1, T2 and T3 represent hydrogels with water uptakes of 4%, 14% and 40% (w/w), respectively

Tumour response and animal toxicity

Injection of solutions of cisplatin to exact doses was at times difficult because of leakage from the tumour. The slow-release rods, however, proved to be extremely easy and quick to implant and avoided leakage problems. No solid remains of the starch rods could be recovered from the tumour by 24 h after implantation. Some erosion was noted in T3 rods at 2 months after implantation; in contrast, T1 hydrogel rods could be recovered apparently intact from the tumour.

The i.t. administration of cisplatin, both as a solution and in slow-release devices, resulted in an increase in the maximum tolerated dose (MTD) as compared with i.p. injections (Table 1). The MTD for i.t. implanted starch rods was almost identical to that for cisplatin solution injected i.t. For the cisplatin-containing hydrogel rods, the MTD increased with decreasing release rate, enabling larger cisplatin doses to be given when they were delivered over longer periods.

Table 2 summarizes the tumour response and animal toxicity caused by the different treatments. Tumour growth delays were slightly higher after i.t. administration of cisplatin solution than after i.p. injection of cisplatin, although the differences were not statistically significant. Rods that did not contain cisplatin had no effect on tumour growth, but implantation of these rods caused a slight reduction in body weight. For the starch rods at cisplatin doses of 12 and 18 mg/kg, tumour responses were almost identical to those obtained with i.t. injections of cisplatin solution at lower doses. Higher doses of cisplatin incorpo-

Table 2. Summary of the effect of cisplatin given by i.p. and i.t. injection and by i.t. implantation of cisplatin in slow-release rods on tumour (tumour growth delay, cures) and normal tissue (peak weight loss, deaths)

Treatment group	Cisplatin dose (mg/kg)	Tumor growth delay (days)[a]	Peak weight loss (%)	Mortality (%)	Cures (%)
Injection, i.p.	0	−0.5 ± 0.4	0.1 ± 0.1	0	0
	3	2.2 ± 1	1.7 ± 0.7	0	0
	6	5.3 ± 1.1	1.9 ± 0.5	0	0
	9	13.2 ± 2.9	11.9 ± 0.5	0	0
Injection, i.t.	0	−0.8 ± 0.5	0.2 ± 0.2	0	0
	1	1.9 ± 1.3	0 ± 0	0	0
	3	4.1 ± 1.4	1.6 ± 0.9	0	0
	5	5.6 ± 1	2.5 ± 1.3	0	0
Starch rods	0	−0.3 ± 0.4	1.2 ± 1.2	0	0
	12	8.3 ± 1.9	6.5 ± 1.9	0	0
	18	8.3 ± 3.3	4.8 ± 1.2	0	0
	24	24.8 ± 5.9	23.7 ± 4.1	40	0
	30	20.7 ± 5.1	21.7 ± 5.1	40	0
	36	–	–	100	0
T3[b]	0	−0.6 ± 0.4	2.6 ± 1.6	0	0
	10	10.6 ± 2.6	8 ± 1.4	0	0
	20	27.6 ± 5.1	12.2 ± 3.6	0	0
	30	19.6 ± 7.4	12.6 ± 2.1	0	20
	40	31.3 ± 12.4	17.3 ± 3.1	40	0
T2	10	3.3 ± 1.2	−0.2 ± 1.7	0	0
	20	16.1 ± 7.6	6.9 ± 1.5	0	0
	30	12.4 ± 2.6	6.5 ± 1.8	0	0
	40	55.6 ± 12.2	19.4 ± 3.6	0	0
	60	–	–	100	0
	80	–	–	100	0
T1	10	3.7 ± 1.9	−1.4 ± 0.9	0	0
	20	2.2 ± 1.2	4.7 ± 2.7	0	0
	30	3.1 ± 0.2	1.8 ± 2	0	0
	40	0.3 ± 0.2	−1.7 ± 0.6	0	0
	60	6 ± 1.3	−0.9 ± 1.7	0	0
	80	5 ± 1.6	2.6 ± 2.3	0	0

[a] Time required for tumours to grow 2 mm in diameter; corrected for control growth values

[b] T3, T2 and T1 represent hydrogels with water uptakes of 40%, 14% and 4%, respectively

Data represent the mean ± SEM of 5 animals

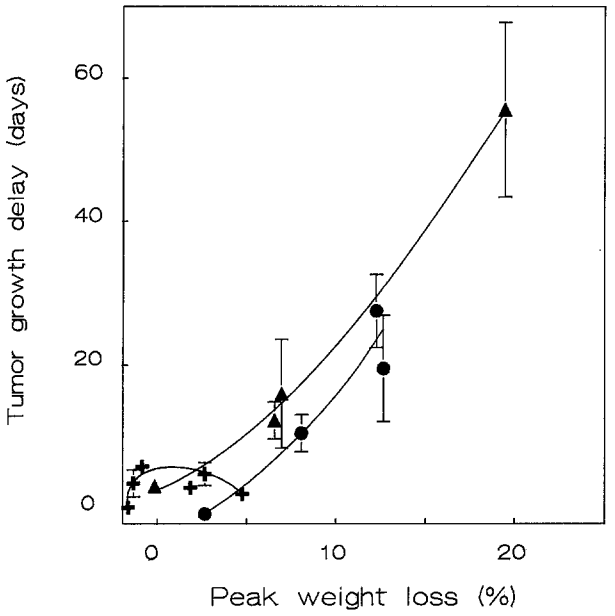

Fig. 3. Analysis of tumor growth delay vs peak weight loss after i.t. administration of cisplatin in hydrogel rods T1 (+), T2 (▲) and T3 (●) (mean ± SEM); ($n = 5$)

rated in starch rods caused death in 40% of the animals. Tumour growth delay in the surviving animals was >20 days.

The slowest-release hydrogel formulation (T1) had very little effect on tumour growth delay or toxicity, even at cisplatin doses 8 times that tolerated as a free bolus injection (Table 2). In contrast, i.t. administration of the fast- and intermediate-release formulations resulted in large dose-dependent tumour responses. Marked reductions in tumour diameter were obtained with T2 rods at cisplatin doses of 40 mg/kg and with T3 rods at doses of 20–40 mg/kg. In the group implanted with T3 rods at a cisplatin dose of 30 mg/kg, 1/5 mice was cured (tumour-free at 5 months after treatment); all other tumours, however, eventually reappeared and showed progressive regrowth.

Tumour growth delay for a given cisplatin dose was highest for the fast-release hydrogels and decreased with decreasing release rate (Table 2). The longest tumour growth delay for a group, however, was obtained with formulation T2 at a cisplatin dose of 40 mg/kg, with no deaths occurring in this group (Table 2). When 40 mg/kg cisplatin was delivered within 2 days (T3), mortality of 40% resulted. Animal toxicity for a given cisplatin dose also decreased with decreasing release rate, as is clear from the weight-loss data (Table 2). Analysis of tumour growth delay vs peak weight loss (Fig. 3) showed that the intermediate-releasing hydrogel formulation (T2) obtained, by a small margin, the highest tumour response for a given level of toxicity.

Discussion

The i.t. administration of cisplatin has been shown to have greater efficacy in controlling local tumours in animals than do systemic routes of administration [8, 22, 31, 32]. Furthermore, systemic toxicity is reduced by locoregional administration, enabling higher doses to be delivered. In this study we gave cisplatin i.t. in implantable polymeric slow-release devices with widely different release rates and found that tumour responses could be further improved using high doses of cisplatin delivered over a period of a few days (T3) to several weeks (T2). The responses were much better than those achieved with i.p. injected cisplatin in this tumour model [8, 10].

The incorporation of cisplatin in a collagen matrix to slow its release from the tumour and localize its effect has been reported to increase tumour growth delays slightly in comparison with i.t. injections of cisplatin solution [32]. In our own studies using this collagen matrix, we found a slight decrease in tumour effect, although systemic toxicities were markedly reduced, resulting in an increase in the therapeutic index for this treatment [8]. Other investigators have found that i.t. injections of a water-in-oil emulsion of cisplatin were also less effective against the tumour than was i.t. administration of cisplatin in aqueous solution but resulted in considerably lower toxicity [31].

A disadvantage of the viscous-fluid collagen matrix is that accurate i.t. dosing was difficult because of leakage from the injection site in solid tumours. This probably results from an increase in i.t. pressure due to the injection of a relatively large amount of fluid; e.g. 0.15 ml was injected into tumours with a volume of approximately 0.5 ml [8]. Other investigators have injected as much as 0.5 ml cisplatin solution into tumours with approximately the same volume [22]. The i.t. administration of such large amounts results in a squeezing-out of injected fluid formulations and the rapid egress of the chemotherapeutic from the tumour into the systemic circulation, leading to a significant exposure of normal tissues. An advantage of the slow-release rods used in the present study is that the interstitial pressure increase is minimal after i.t. implantation of these rods, which have a volume of <9 µl, i.e. approximately 4% of the tumour volume. Further advantages of solid slow-release systems include more precise location and dosing and the exposure of tumour cells to high concentrations of chemotherapeutic over extended periods.

In the present study, marked reductions in tumour diameter were obtained using hydrogel rods made of polyether polymers, which released cisplatin over a few days (T3) to a few weeks (T2) at doses near the MTD for these treatments. Eventually, most tumours regrew, but tumour regrowth delays were long. Considering the marked and often complete regressions observed, the released drug was evidently cytotoxic and not simply cytostatic, consistent with many in vitro studies. From the volume-doubling time of approximately 2.5 days for this tumour, the magnitude of cell killing could be calculated from the specific growth delay (delay/doubling time) as being >99% for the treatments, giving growth delays of >25 days. This estimate is only approximate and depends on the assumption that the average proliferation rate of surviving cells equals the pretreatment volume-doubling time. In principle, the translation to cell killing is independent of whether the killing took place instantaneously (e.g. with radiation) or over several days, as occurred in the present study [6].

Despite possible calculation uncertainties, the regressions and long growth delays indicate that active drug was distributed to most areas in the tumour. A sufficiently homogeneous drug distribution within the tumour for optimal effect may still be a problem, however, since it has been demonstrated that the penetration depth for cisplatin in peritoneal tumours is between 1 and 2 mm after i.p. chemotherapy [18]. Our studies on s.c. tumours confirm this finding and will be reported elsewhere. Optimal spacing of rods is therefore critical for maximal antitumour effects.

Starches have been studied extensively as release-modifying matrices. Release from such hydrophilic matrices is generally considered to be limited by diffusion of water into and diffusion of dissolved drug out of the matrix [4]. Degradable starch microspheres have been applied as occlusive hydrophilic gels after intra-arterial delivery and were reported to be well tolerated [2, 17]. Degradation of starch occurs through the action of amylases. In the present study, no solid remains of the starch rods could be recovered from the tumour at 24 h after i.t. implantation. It can be anticipated that starch will be non-immunogenic in its native soluble form, and all immunological tests performed thus far support this assumption [12]. These obvious advantages of a starch-based system are counteracted, however, by the rather fast release of cisplatin observed from the particular formulation used in the present study, which did not result in an increase in tumour response over that obtained after i.t. injection of cisplatin solution. Formulation of slower-release starch systems is being attempted.

The polyether hydrogels used in this study released cisplatin over much longer periods than did the starch rods. Altering the water uptake of these systems by changing monomer blends proved to be an easy method of varying the release over a period of 1 day to several weeks. Generally, hydrogels are considered to be biocompatible materials [24]. However, the hydrogels used in the present study and most other studies are not readily biodegradable and should therefore be removed after all drug has been released. Biodegradable cisplatin-containing implants prepared from lactic acid/glycolic acid copolymer have been described that shown in vivo release over approximately the same period achieved in the present study with T2 hydrogel rods [14].

In the present study, drug release from the slow-release devices was higher in the first few days after i.t. implantation, decreasing as the slow-release devices became empty. These systems were shown to be effective in reducing tumour diameter and increasing tumour growth delay, but systems that release cisplatin over the same period with zero-order release, exposing tumour cells to high levels of drug over the entire release period, may prove to be more effective.

We conclude that local tumour response can be markedly increased by i.t. implantation of cisplatin in slow-release systems. Release of cisplatin from such systems over a period of 3–4 weeks resulted in the highest tumour response at a given level of animal toxicity. Further studies are being aimed at the development of more biodegradable implant systems and at improving their efficacy when they are used in combination with X-irradiation.

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