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BRAIN TUMOUR: METHODS OF TREATMENT

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ABSTRACT

Primary brain tumors have a significant infiltrative capacity as their reappearance after resection usually occurs within 2 cm of the tumor margin. Local delivery method such as Convection-Enhanced Delivery (CED) has been introduced to avoid this recurrence by delivering active molecules via positive-pressure Methods and discuss the technical approach of CED with regard to catheter design and brain characteristics; secondly, we will describe the 'ideal' nanocarrier in terms of size, surface properties, and interaction with the extracellular matrix for optimal diffusion in the brain parenchyma. We also discuss preclinical and clinical applications of this new method. The role of PET in the visualization of the biological characteristics of the tumours: proliferation (FLT-PET), hypoxia (FMISO-PET) and angiogenesis/ peptide expression (RGD-PET) should be investigated in future studies.

Keywords: Convection-enhanced delivery, Nanocarrier, Anticancer treatment Glioblastoma, Viral vectors, Suicide genes, Brain tumors, Radiation treatment planning.

INTRODUCTION

The appropriate management of brain tumors requires a combination of surgery, radiotherapy (RT) and chemotherapy. Whenever possible, patients should be referred to specialized centers, where different specialists with training in the field of neuro-oncology devote their efforts to these types of neoplasm Nowadays, according to the World Health Organization (WHO) classification of brain tumors issued last year [1], the histological diagnosis of a brain tumor must be completed by an immune histochemical analysis and, preferably, by an assessment of chromosomal or other genetic alterations which may identify different subtypes of glial tumors and predict clinical outcome and response to therapies. The prognostic role of these genetic alterations, however, is not yet clear. In oligo dendrogliomas, on the contrary, allelic loss of chromosomes 1p and 19q is now a recognized predictive element for durable responses to chemotherapy and prolonged survive.

Recently, it was shown that fluid convection, established by maintaining a pressure gradient during interstitial infusion, can supplement simple diffusion to enhance the distribution of small and large molecules in brain and tumor tissue. This technique called Convection-Enhanced Delivery (CED) was proposed and introduced by researchers from the US National Institutes of Health (NIH) by the early 1990s to deliver drugs that would not cross the BBB and that would be too large to diffuse effectively over required distances. In this case, in situ drug concentrations can be significantly greater than those achieved by systemic administration. This technique allows the local delivery of a wide range of substances like conventional chemo therapeutic agents, monoclonal antibodies, targeted toxins, other proteins, viruses, and nanocarriers. During the first decade after the NIH researchers founded this analytical model of drug distribution, the results of several computer simulations that had been conducted according to realistic suppositions were also published, revealing encouraging results

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DIFFERENT TECHNIQUES IN BRAIN TUMOUR TREATMENT

PET (Positron Emmision Tomography) Technique

In brain tumors, treatment planning and the evaluation of local response to therapy are usually based on

magnetic resonance imaging (MRI) and computed tomography (New concepts such as pseudo-progression or pseudo-remission were introduced for brain gliomas, underscoring the fact that conventional MRI is insufficient for the visualization of tumor tissue after therapy [2].

New MRI methods such as diffusion and perfusion MRI are promising; however, histo pathological data validating the sensitivity and specificity are scarce.

Hence, routine integration of diffusion or perfusion MRI in radiation treatment planning is premature. MRI spectroscopy has a long tradition but, unfortunately, the method remains relatively laborious and has a low resolution.

Therefore, there is an urgent need for new imaging approaches to increase accuracy in tumor delineation for high precision radiotherapy. Positron emission tomography (PET) is an interesting approach to improve treatment planning for high precision radiotherapy.

In the first part of this chapter we will discuss the role of amino acid (AA)-PET for gross tumor volume (GTV) delineation in brain gliomas, metastases and benign cranial tumors such as meningiomas and glomus tumors. In the second part, we will focus on tracers used to visualize biological properties of tumors such as hypoxia, proliferation or expression of peptide/protein on the cell membrane.

Brain gliomas

11C-labelled methionine (MET), 123I-labelled alpha-methyltyrosine (IMT) and 18F-labelled O-(2)fluoroethyl-L-tyrosine (FET) are the most important radio-labelled AA used in the diagnosis of brain tumours. These three tracers were shown to have a very similar.

The higher diagnostic accuracy of AA-PET is the rationale for using this technique in target volume delineation of gliomas, since AA-PET can also provide information regarding tumour extension In a series of clinical studies, marked differences between AA-PET or SPECT and MRI in GTV delineation for radiation treatment planning have been demonstrated [3].

In 39 patients with high-grade gliomas imaged postoperatively, tumour contrast enhancement in MRI and MET uptake corresponded in only 13% of the patients. On average 13 ml (33%) of the tumour volume defined on MET-PET Weber *et al*. [4] assessed the failure pattern observed after FET planning after chemo- and radiotherapy for high-grade glioma.

There are some data in the literature showing that AA-PET could be of interest in the differentiation between recurrent tumours and treatment-related changes in brain metastases treated with stereotactic radiotherapy/ radiosurgery [5]. In meningiomas, the GTV is routinely delineated using the contrast enhancement areas on CT and MRI, and bone windowing on CT-unstated no contrast .Using MET PET/CT-fused images, meningioma borders can be delineated more accurately with respect to normal tissue [6]. The inter-observer variability in the GTV and PTV definition can be significantly reduced [7]. Similar observation were made using [68 Ga] -labelled DOTA (0)-D-Phe (1)-Tyr (3)- Octreotide (DOTATOC)-PET [8]. Gluc-Lys [(18)F]-TOCA- or DOTATOC-PET were also used in the GTV delineation for stereotactic radiotherapy in glomus tumours .enhancement on MRI intensity and distribution in brain tumour .Visualization of tumour biology: FLT-PET, FMISO-PET and RGD-PET Proliferation of tumour cells is the basic mechanism for malignant growth. [18F]-Fluorine labelled thymidine analogue 30- deoxy-30-[18F]-fluorothymidine (FLT) is retained in the cell after phosphorylation by thymidine kinase 1, whose levels correlate with cell proliferation. The kinetics of FLT uptake in malignant gliomas correlates with the expression of avb3 integrin can be visualized with F18-labelled RDG-containing glycopeptide, which binds to the avb3 receptor [9] avb3 integrin is blocked by cilengitide, a new drug under investigation in the treatment of high-grade gliomas. The intensity modulated radiotherapy (IMRT) combined with a treatment plan based on biological imaging could be used for individualized, i.e. customized radiation therapy. This approach has been named dose painting.

CONVECTION ENHANCED DELIVERY (CED) OF NANOCARRIERS TECHNIQUE

It is a novel approach to deliver drugs into brain tissue and is defined as the continuous injection of a therapeutic fluid agent under positive pressure. This recent technique using convection or 'bulk flow' was proposed to supplement simple diffusion which characterizes local intra cerebral delivery by stereotactic in Diffusion is defined as a type of passive transport (non-energy requiring) involving the movement of small molecules from an area where they are highly concentrated to an area where they are less concentrated. The diffusion of a compound in a given tissue depends mainly on 2 parameters: the free concentration gradient and the diffusivity of this compound in the tissue. With the classic diffusion technique, high molecular weight compounds (neurotrophic factors, antibodies, growth factors, enzymes) are not able to diffuse over large distances and drug distribution is very limited, thus reducing the treatment efficacy of neurological disorders.

For example, 3 days can be necessary for an IgG to diffuse 1 mm from its delivery site. Moreover, small drugs with good diffusion characteristics can be metabolized or quickly eliminated by capillaries reducing their diffusion in surrounding tissues [10].

On the contrary, CED is powered by bulk flow kinetics which occur secondary to pressure gradients. Convection, which can be used to supplement diffusion, relies on a simple pressure gradient, and is independent of molecular weight. In practice, drugs are delivered continuously via a catheter connected to a syringe pump, thus enabling the distribution of large volumes of high drug concentrations with minimum systemic toxicity injections

CED is a complex process that is governed by many parameters. This review aimed at listing the technical parameters directly linked to delivery by convection and especially to the volume of distribution (Vd), and the control of the backflow mechanism Gray matter is mainly composed of the somas of neurons and glial cells. The effective diffusivity in gray matter is almost the same in all directions, and the transport in the gray matter is qualified as isotropic (Fig. 3). White matter contains bundles of axons leading to the peripheral nervous system. The permeability of the white matter changes in accordance with directional alignment and density of axon. Hence, white matter diffusion is anisotropic. A widespread of agents can be achieved in both white and gray matter, but white matter exhibits a greater ability to accommodate infuscate because it is more densely packed and there is less extract 2.2.2. Catheter placement Catheter placement is very important for several reasons and especially for preventing the occurrence of backflow. Backflow can lead to the spreading of the agent into regions of the brain where it is not intended to be and, possibly, to a diminution of the dose otherwise needed within the target tissues. The problem can be particularly acute in cortical infusions, when backflow of the agent along the insertion track and into the subarachnoid space can occur, with the subsequent widespread distribution of the agent via the circulating cerebrospinal fluid (CSF) [11].

Raghavan described an example which illustrates the leakage of an infused agent into the subarachnoid space via backflow into the Rate of infusion – catheter size the pressure gradient, which generates the convective movement, is equal to the difference between the skull pressure and the injection pressure. The flow of injection is thus a critical parameter to create convection, and it is known that it is related to the resistance of the considered tissues (gray and white matter). Finding an optimal infusion rate for CED has been elusive because it is often limited by the development of backflow along the cannula track. In most cases, the optimal infusion rate is that which allows the delivery of the therapeutic volume over the least amount of time without any associated reflux. This optimum is Catheter design the use of a reflux-free cannula in order to enhance the infusion rate of therapeutic agents by CED has been described, thus reducing the duration of treatment and, by the way, the exposure of patients to high risk of infection or side effects also dependent on the cannula size used. In general, the higher the infusion rate and catheter diameter used, the greater the reflux induced. To obtain effective convection in rodent models, the injection flow must be in the range of 0.5–5 ml/min. Indeed, weaker flows limit the extent of the distribution volume, whereas too high flow facilitates backflow. In addition, the use of superior flow levels is not recommended as the generated hydrostatic pressure can damage the tissues. Consequently, the use of a 0.5 ml/min rate of infusion is often described to carry out effective CED in rodent. Kroll *et al*. underline that the infusion rate has to be adjusted.

Heart rate enhancement

In order to increase the distribution volume, it should be possible to enhance brain fluid circulation by enhancing the level of this circulation. Hadaczek *et al*. hypothesized that infusate distribution is caused by brain fluid circulation which is itself generated by arterial pulsations [11]. They evaluated the Vd of 7.2 nm-bovine serum albumin (BSA), 65 nm-fluorescent liposomes. Rats were randomized in three groups: group H with high blood pressures and heart rates induced by epinephrine, group L with low blood pressure and heart rate induced by blood withdrawal, and group N with no heart action. They found first, that whatever the nature of the infusate, the Vd was significantly higher for group H compared to group L and group cording to the model used catheter during the infusion.

The convection-enhanced delivery of nanocarriers

Nanocarriers are constructed systems that are measured in nanometer size (nm) and that can carry multiple drugs , radio nuclides and/or imaging agents Nanomaterials for drug delivery include various architectural designs in terms of size, shape and materials. The characteristics of each nanocarrier differ in structure composition, drug-loading capacity, ability to Nanocarrier labeling Nanocarriers can be labelled by incorporating a marker in the liposomal/nanoparticle membrane and/or can be loaded by encapsulation of a marker within their interior part. Such applications involve the use of histological The ideal conditions are obtained when nanocarriers can be labelled and loaded by two kinds of markers, thus excluding the possibility of a distribution linked to the marker released from the carrier. Moreover encapsulate hydrophobic or hydrophilic molecules, carrier stability

Nanocarrier physicochemical properties

In this, we will focus on the parameters influencing nanocarrier's aptitude to diffuse to be diffused in brain parenchyma, depending on their size, charge, composition, surface properties, and physicochemical characteristics. All these data are resumed Size Many studies have focused on the optimum in size for nanocarriers used in CED. The conclusions are quite unanimous since the distribution volume of nanocarriers in rat striatum is inversely proportional to the size of the particle. Mackay *et al*. worked on the physicochemical properties of liposomes in order to optimize post- CED diffusion [12].

They concluded that ideal liposomes for CED should be less than 100 nm in diameter, because above this size, liposomes are retained near the site of injection and are characterized by restricted mobility. Studies on brain

extracellular space (ECS) gave more precise informations: the ECS has been estimated at between 35 and 64 nm in diameter in normal rat brain which means that many vectors beyond 100 nm will be too large to transit normal neocortical extracellular space. The size of some polystyrene nanospheres administered by CED was also evaluated in rats in order to mimic the behavior of viral vectors

Concentration

The concentration of the infusate had no impact on the calculated Vd, nor on the global distribution of the infusate in brains [13]. Indeed, when the 14C-BSA concentration increase brain affinity. The use of co-infusates (e.g. heparin, basic fibroblast growth factor or mannitol) has been widely described as reducing the affinity of infusates to the brain environmentd from 25 to 50 and 100%, the corresponding.

FUTURE TRENDS IN BRAIN TUMOUR TREATMENT

Future trends for high grade gliomas preferably, the surgery performed is as extensive as possible, although this depends on the site of disease and the neurological performance of the patient. By means of ultrasound aspirator and microsurgery techniques, perioperative morbidity and mortality at present are low, albeit not completely absent.

No clinical trial has as yet demonstrated a consistent advantage of neo-adjuvant chemotherapy delivered before RT [14], even though this is probably the most suitable setting to evaluate the activity of new drugs Hyper fractionation regimens or accelerated RT schedules have been studied in randomized trials, without significant benefit. Likewise, brachytherapy has not been shown to increase overall survival (OS) and causes a higher incidence of symptomatic radiation necrosis [15]. Today, the main perspectives of research in the field of radiotherapy of brain tumors are

The development of effective radio-enhancers: for instance, an allosteric modifier of hemoglobin, RSR13, increases oxygen release in peripheral tissues; it is administered 30min before radiotherapy concomitantly with inhalation of oxygen [16]. The use of radio surgery, which is under investigation in the European Organization for Research and Treatment of Cancer (EORTC) 22972/MRC BR10tri al in which patients with high grade gliomas are randomized after surgery to receive or not a 20Gy/4 fractions stereotactic boost after standard RT. The concomitant administration of chemotherapeutic drugs synergistic with RT (such as temozolomide).

- Boron Neutron Capture Therapy, consisting of administration of a B10 carrier (such as boron-Phenylalanine) that crosses the brain–blood barrier and accumulates in the tumor cells TMZ, an imidazole derivative that alkylates DNA, is the most promising new drug in recent years, with an optimal profile of clinical tolerability, even in elderly patients. Response rates range from 5.4% [17] to 23.8% [18] in Glioblastoma patients, with a progression-free survival at 6 months (PFS-6) of 26% and 31.8 % High-dose chemotherapy with autologous stem cell. Current approaches that aim at inhibiting AGT and enhancing cytotoxicity of BCNU and TMZ are: rescue did not prove advantageous for high grade gliomas patients, perhaps with the exception of medulloblastoma [19]. Today, most efforts are directed towards the development of new drugs or alternative strategies to overcome drug resistance

- Pre-exposure to other agents that alkylates guanine in the O6 position, and saturate AGT in the tumor cells. A phase II study was conducted by Brandes and colleagues [20] in 58 glioblastoma patients at first recurrence (after surgery and radiotherapy) who were treated with procarbazine (100 mg/m2, on days 1–5), vincristine (1.4 mg/m2, max 2 mg on day 3) and BCNU (80mg/m 2 on days 3–5), every 8 weeks. A response rate (complete and partial response (CR+PR)) of 29% was obtained, PFS-6 was 42.3% (95% confidence interval (CI): 31.2–57.3%), and median OS was estimated to be 13.8 months.

Future trends for low-grade gliomas

According to the randomized EORTC 22844 trial, early RT delays progression, but does not improve survival in these patients, and lowdose treatments (up to 45 Gy) seem to be as effective as the standard 60Gy dosage [21]. Low-grade gliomas respond to chemotherapy [22]. For these patients, however, clinical improvement is usually the major endpoint, instead of a radiological shrinkage of tumour extension, which, indeed, is often difficult to achieve. If RT is postponed, neuro-psychological functions remain unchanged [23].

Primary central nervous system lymphoma

The role of intrathecal MTX remains uncertain, as well as the need to add ARA-C or other cytotoxic drugs to MTX, which was confirmed to be the most effective drug. In patients that achieve a CR after chemotherapy, consolidation with whole brain RT may be postponed, n or substituted with further monthly cycles of MTX.

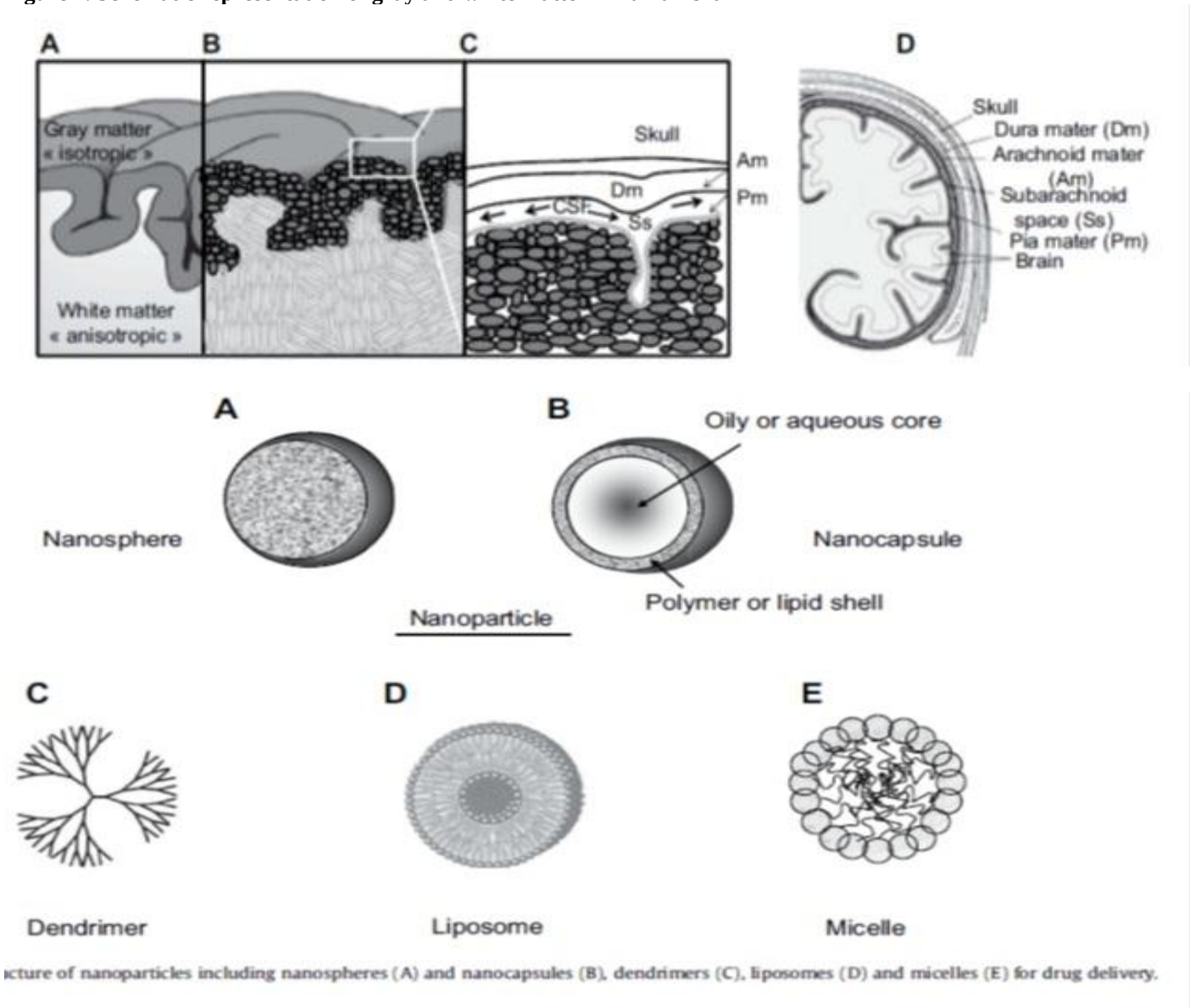
This approach appears to be particularly advantageous in elderly patients, who are more susceptible to the A.A. Brandes *et al.* damaging effects of large fields of radiation to the brain [24]. In fact, in a recent study conducted at the Memorial Sloan Kettering Cancer Centre (MSKCC) [25], non irradiated patients >60years had the same survival as irradiated elderly patients, most of whom died because of RT-induced leucoencephalopathy without any sign of recurrement.

Future direction and development :

In fact, advances in the knowledge of the molecular events that underlie tumour formation and invasion prompt the researchers to develop molecules that target the specific pathways altered in glioma cells, for example the activation of membrane or cytoplasmic kinases (such as EGF receptor, protein kinaseC and cyclin-dependent kinases (CDKs), the loss of physiological checkpoints in the cell cycle (such as p53 and p105Rb), and the production of growth factors (PDGF and insulin-like growth factor (IGF)), angiogenic factors (vascular endothelial growth factor (VEGF) or m*et al*oprGene therapy is a modern and innovative strategy of treatment for glioblastoma multiforme; small clinical trials showing some responses and no important side effects. Side effects have already been carried out. The association of a suicide gene, such as the Herpes Simplex TK, with immune modulating cytokines**,** such as interleukin (IL)- 2 or IL-4, so-called immune gene therapy, is an alternative strategy.

Short penetration of the gene vector in tumour nodules is responsible for low transfection efficacy in vivo, and this is probably one of the major obstacles to a strong and long-lasting anti tumour effect by gene therapy. Liposomes or systems of convection-enhanced injection will probably allow the potentiation of the delivery of genetic material to glioma cells in vivo, and positron emission tomography (PET) may be extremely useful to monitor the process of gene transfer in vivo.

Figure 1. Schematic representation of gray and white matter in human brain



icture of nanoparticles including nanospheres (A) and nanocapsules (B), dendrimers (C), liposomes (D) and micelles (E) for drug delivery.

CONCLUSION

Local delivery of agents to brain tumors by Convection- Enhanced Delivery offers the advantage of better drug distribution compared to other strategies only governed by diffusion. Because this technique was also characterized by the appearance of side effects caused by backflow along the catheter and drug leakage in non-desired regions, the encapsulation of active molecules within the concept of CED has been investigated to overcome this problem.

The encapsulation of such a drug, a toxin, or a gene is under investigation on experimental models rather than in clinical trials, but seems to be very promising for the treatment of brain malignancies and Extensive research devoted to the understanding and to improving the treatment of malignant gliomas over the past three decades has yielded few, but important, advances.

One of these is insight into the origin and biology of brain tumours. A remarkable increase in the number of new agents being developed that are aimed at either the cell cycle, signal transduction, receptor membranes or inhibiting invasion of brain tumour cells has become apparent.

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