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Review

Photodynamic therapy of cerebral glioma – A review Part II – Clinical studies

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Abstract

Photodynamic therapy (PDT) is a binary treatment modality that has been used to treat malignant brain tumours for 25 years. The treatment involves the selective uptake of a photosensitizer (PS) by the tumour cells followed by irradiation of the tumour with light of the appropriate wavelength to excite and activate the PS resulting in selective tumour destruction and is a potentially valuable adjunct to surgical excision and other conventional therapies. PDT has undergone extensive laboratory studies and clinical trials with a variety of PS and tumour models. These are discussed with reference mainly to clinical studies involving the PDT of brain tumours.

Keywords: Brain tumours; Glioma; Photodynamic therapy; Haematoporphyrin

1. Introduction

Approximately 2% of cancer deaths can be attributed to brain tumours and in the United States, 18,000 new cases of primary brain tumours are estimated to occur every year.[1,2] The complex biology of the brain tumour and in particular, the ability of the tumour cells to invade adjacent normal brain tissue diffusely beyond the surgical resection leads to local recurrence and a poor prognosis for the glioma patients.

As these tumours infiltrate diffusely into the surrounding brain, it is clear that adjuvant therapies that target the infiltrating cells must be developed to augment surgical resection. A multi-modal treatment approach usually involves maximal surgical resection, radiotherapy and chemotherapy as the standard of care, but the majority of malignant gliomas recur within 2 cm of the original tumour location[3] as there is a failure of local control of the tumour by conventional treatments, thus a more aggressive local treatment would be of value. Only a very small minority of patients achieve a longer term of survival.[4] The median survival time for high grade glioma is less than 12 months following treatment with surgery, radiotherapy and chemotherapy.[5] The biological basis for photodynamic therapy (PDT) and the laboratory studies undertaken to investigate the mechanisms of the therapy were discussed in the Part I review.[6] In Part II we review the clinical studies of PDT used to treat high grade glioma.

2. Photosensitizers

Thousands of patients have been treated with PDT for a variety of neoplasms since Perria treated his first glioma patient in 1980 (Table 1). Even though numerous photosensitizers (PS) have undergone laboratory and pre-clinical investigations in the last 20–25 years (Table 2), the bulk of clinical experience in PDT has been with the porphyrin based photosensitizers haematoporphyrin derivative (HpD) and its purified form, Photofrin.[7–42] The series of PDT of gliomas listed in Table 1 have used either HpD or Photofrin as a PS and the dose range in these clinical studies has been between 2 to 5 mg/kg for both with variations in the light doses.

Photofrin was first given regulatory approval for PDT in 1993 by the Canadian Health Agency for the treatment of

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Table 1
Photodynamic therapy glioma clinical series

Study	Patient number	Fibre ouput (W)	Total light dose / Light source (J)	Dose per unit surface area (J/cm^2)
Perria et al. [94]	9	0.025	NA / He laser	0.9–9
Perria et al. [98]	8	0.06-0.4	720–2400/ He laser	NA
McCulloch et al. [130]	16	0.280–0.460	1620–2520 / Ar/dye/lamp	NA
Wharen et al. [135]	3	NA	Ar/dye/lamp	180
Laws et al. [96]	5	0.250–0.400	540–1440/ Ar/dye	NA
Muller and Wilson [93]	50	0.175–1.00	439–3888 / Xe lamp	8–175
Origitano et al. [122]	15	1.0–4.0	140–14300 / Ar/dye	50
Kostron et al. [91]	51	NA	320–1200 / Ar/dye / lightsource	15–260
Kaneko et al. [132]	22	NA	NA / Copper dye	NA
Stylli et al. [95]	358*	0.4–4.0	NA / Ar/dye; Gold metal vapour laser; KTP-YAG dye pumped	70–240

NA – Total light dose range not available.
* 136/358 total patients who were resident in the State of Victoria and had their deaths verified with the Victorian Cancer Registry and reported in this reference. 358 patients in total have been treated at the Royal Melbourne Hospital.

Table 2
Selected photodynamic therapy trials for various photosensitizers

Photosensitizer	Indication	Reference
Aminolevulinic acid	Basal-cell carcinoma, Barrett's oesophagus, cervical intraepithelial neoplasia	136–141
Photofrin	Barrett's Oesophagus, non-resectable cholangiocarcinoma, intraperitoneal tumours, pituitary adenomas,pleural mesothelioma, gliomas	18,92,93,99,102,142–146
Mono-L-aspartyl chlorine e6	Squamous cell carcinoma, basal-cell carcinoma, papillary carcinoma, adenocarcinoma	84,147,148
Haematoporphyrin derivative	Papillary transitional cell carcinoma, refractory carcinoma in situ, glioma, pleural mesothelioma,	13,95,103,119,149,150
Purlytin (Tin etiopurpurin)	Recurrent breast cancer	58
Foscan (temoporfin, mTHPc)	Pleural mesothelioma, gastric cancer, ovarian cancer, basal-cell carcinoma, squamous cell carcinoma	81,151–154

bladder cancer. Since that time, preclinical studies have allowed for subsequent approvals in oesophageal cancer[43] and lung cancer[44–48] in countries including Canada, the United States, Japan, France, Germany, Finland, Denmark, Iceland and the United Kingdom. Photofrin trials for other indications are pending regulatory approval.[49–57]

Factors to consider when evaluating a new PS over the current generation PS are that they must possess some if not all of the following properties to be considered as viable options for the next generation of PS. These properties include pure composition, water solubility, tumour cell selectivity, activation at longer wavelengths for increased tissue penetration and effective treatment area and reduced skin phototoxicity. The first generation, HpD and Photofrin, suffered from the drawbacks of prolonged patient skin photosensitivity and activation extending up to 630 nm.

Promising results have been obtained in laboratory and pre-clinical studies with many second generation PS for a variety of indications due to their improved properties and characteristics over the first generation porphyrins. These include Purlytin,[58,59] Lutetium Texaphyrin,[60–64] Benzoporphyrin Derivative – Monoacid Ring A (BPD-MA),[65–72] Tetra (m-hydroxyphenyl) chlorine (mTHPC),[73–83] N-Aspartyl chlorine e6 (NPe6)[84–87] and phthalocyanines.[88–90]

3. Laser light and tissue penetration

As PDT depends on light delivery to tumours that have selectively taken up the PS, the type of light source coupled with an appropriate delivery system are important. Lamps and lasers have been both employed to perform PDT and the choice of light system is dependent on the site of the treatment area and the type of application. Lasers have been the preferred system as they provide a highly coherent, monochromatic, powerful source of light that can be focussed at the target area and produce a significant number of photons to optimally treat the site. In general, the monochromatic property of a laser is crucial as it is specific for one or a small family of PS that have a very narrow bandwith for excitation such as HpD, Photofrin and Porphyrin. At present, lasers are the only possible light source to treat tumour sites that can only be reached with an optical fibre. A variety of laser systems have been constructed over the years with the argon and metal vapour lasers the original choice, especially for PDT of brain tumours.[91–105] The argon-ion pumped dye lasers were initially very popular but they required a high level of technical support due to critical alignment of a narrow cross-sectional beam, possessed an inefficient coupling system resulting in a significant loss of light during delivery and they were relatively immobile. The metal vapour lasers are still being used for treating many types of conditions with PDT. This group of lasers which were usually the gold (producing a laser line at 628 nm) or copper vapour metal laser (which produced two laser lines at 511 and 578 nm in turn pumping a dye to produce light at 630 nm) were relatively mobile and they also produced a higher output of pulsed laser light. However, the high temperature required to produce the metal vapour meant that a bulky and complex pump

and cooling system was vital to keep the laser operational via labour intensive procedures. In our series of PDT treated glioma patients, the gold metal vapour laser has been used up to a fibre output of 4 W.[95] We have also used a frequency doubled ND:YAG KTP pumping a kiton red dye since 1993 in the same series[95] as this type of solid state laser offers a more compact design and is pulsed at higher rates with shorter pulse widths than the metal vapour lasers. They can also offer a wider spectrum of wavelengths depending on the dye-system supplied with the laser.

Since 2004, we have used a diode laser which is constructed of semiconductor based arrays and can produce relatively high output of light at 630 nm while remaining fairly compact and is becoming the system of choice.

Femtosecond solid state lasers are still being used for research in the field of two photon excitation[106,107] but are potentially useful for clinical PDT because light of high photon density in the 800–900 nm region can be used to excite porphyrins in the 400–500 nm region where they have maximal absorbance. The use of wavelengths in the range of 800–900 nm in the two photon excitation process would allow for treatment beyond the penetration depth of the currently used 630 nm with HpD or Photofrin. Svaasand and Ellingsen have shown that a higher penetration depth of light in this region is found amongst glioblastoma multiforme (GBM) and anaplastic astrocytomas (AA).[108] The penetration in the red part of the spectrum is approximately 2–3 times that of the UV region of the spectrum and the penetration in the near-infrared region is typically twice that at the clinically used 630 nm for HpD and Photofrin.

We conducted laboratory investigations in the use of an alternative second generation PS, aluminium tetrasulfonated phthalocyanine (AlSPc) with a longer excitation wavelength of 675 nm in the PDT of malignant glioma.[109] AlSPc showed a selective uptake in an intracerebral xenograft mouse model[110] and PDT induced necrosis in a intracerebral rat model[109] of tumour up to 200 J/cm^2.

The depth of the activating light into the target tissue is a primary determinant of the tumouricidal depth of PDT. The depth and the degree of light penetration through tissue is a function of the wavelength of light and the optical properties of the tissue. Light penetration decreases exponentially as a function of distance and the penetration depth of light into tissue is defined as the depth at which the incident light is reduced to 1/e or 37%, which in practical terms results in an effective necrosis depth of approximately three times the light penetration depth.[108,111,112] However, the vascular effect of PDT must also be considered in addition to direct cellular necrosis depending on the type of PS.

4. Light dosimetry

The PDT response is reliant on a complex relationship between a PS, oxygen and light and great importance has generally been placed on the PS uptake and localization and the amount of oxygen present in the tumour tissue to trigger the PDT effect once activated by light. It is now accepted that the extent of the tissue response to PDT is controlled by the local PS concentration, light dose and oxygen concentration, and that there appears to be a threshold level for this process.[113–115]

Since the work of Perria in 1980,[94] patients with glioma have been treated with PDT primarily using a hematoporphyrin based PS such as HpD, Photofrin or Photosan. The early series of PDT used low light powers up to 400 mW and lower total light doses than the RMH series.[95] The lower total light doses in the early series may be a result of the type of light source used such as the Argon Ion dye pumped laser or xenon arc lamp source, or the concern that higher total light doses may lead to cellular toxicity especially in surrounding normal brain. We have shown previously that the higher total light doses were well tolerated.[116,117] Kostron et al.[118] using porphyrin based PS at clinically relevant doses of between 2 to 5 mg/kg, observed few morphological changes in normal human brain. Muller and Wilson[93] showed that when their patients were categorized either below or above the total dose of 1700 J, the patients with a light dose above 1700 J had a 39% increase in survival. A similar trend was observed in our PDT series where a better prognosis was observed with an increase in the total light dose greater than or equal to the median of 230 J/cm^2 for all primary tumours.[119]

5. Tumour light delivery

The evolution of light sources and delivery systems is critical to the progression of PDT in the medical field. A number of different techniques have been used to deliver light to sensitized glioma tissue for the PDT process. These include two types of intracavitary techniques : (a) shining light uniformly from an open flat cut fibre into an excised tumour cavity through a light diffusing medium such as an aqueous suspension of lipid droplets[95,103,119] and (b) illuminating the tumour cavity through a balloon like device which has also been filled with a light diffusing medium.[93,102,120] A third technique involves the stereotactic placement of multiple fibres into the tumour bed which is also known as interstitial PDT.[97,121]

5.1. Interstitial PDT

A study by Powers et al.[97] using interstitial PDT on recurrent GBM patients showed that the majority of the patients had tumour recurrence within 2 months of the treatment. Even though the PS levels in the 'brain adjacent to tumour' (BAT) region were deemed to be adequate in relation to the amounts present in the tumour, a lack of PDT response in the BAT area could have been due to a suboptimal light dose. Origitano and Reichman[122] undertook a Phase I investigation utilizing a computer assisted image based system to investigate surgical and treatment parameters during PDT and also allowing for the stereotactic

placement of the optical fibres within the tumour. As seen earlier in the study by Powers,[97] treatment failures appeared to occur outside the region of the effective light treatment. Cheng et al.[123] reported an effective radius of tumour cell kill in 22 glioma patients of 8 mm compared with the 1.5 cm depth of necrosis noted by Perria with the intracavitary illumination method.[94]

Krisnamurthy et al.[121] also employed interstitial PDT to treat GBM and AA patients. The primary goal of this study was to determine the maximal tolerable light dose for patients undergoing interstitial PDT with Photofrin. They concluded that increasing the total light dose above 4000 J did not limit the risk of tumour recurrence or prolong survival, but did increase the risk of post-operative neurological deficit.

It has been shown in laboratory investigations that if the surface irradiance exceeds 200 mW/cm^2, it is possible that hyperthermia may synergistically contribute to the overall PDT effect.[112,124–128] For interstitial PDT, the hyperthermia limit has been shown below 400 mW/cm fibre diffuser output. Beyond this, it is possible to expect intratumoral temperature rises of between 5 to 10 °C within 2.5 – 4.5 mm tissue depth from the diffuser.

Although the concept of using interstitial PDT for deep irresectable gliomas, such as those situated in the thalamus or basal ganglia is appealing, there is a concern regarding the exact dose that is delivered, and the consequences of using PDT if the tumour has not been resected. The dosimetry problem relates to the measurement of light administered with charring of the fibre within the tissue reducing the affected expected dose on the one hand, and the inherent problems of inequality of dose to tissue related to the implantation of fibres, even utilising multiple beams. This would mean that some parts of the tumour might incur very high doses of light, but others have a sub-optimal (sub therapeutic) dose.

In addition, it is known that PDT will cause some degree of cerebral oedema, although this is usually relatively easily controllable with steroids, provided there has been an adequate tumour resection. It is our belief that a tumour resection is important in order to create a cavity to allow for local brain swelling. In addition, it is likely that toxic products released by breaking down tumour cells are the basis for cerebral oedema that follows PDT. If there has been a maximal tumour resection, the number of tumour cells remaining to treat and release of toxic cellular products are minimised. Of course, with stereotactic implantation of fibres for PDT, there is not only no cavity for the brain to swell into, but also the considerable volume of tumour to undergo necrosis, and consequently cause increasing cerebral oedema.

5.2. Intracavitary illumination with balloon devices

Origitano and Reichman[122] also treated a small group of patients via intracavitary PDT using a balloon filled with an intralipid solution which was a modification of a balloon application that was used earlier by Muller and Wilson.[102] There was no significant difference in survival between the interstitial and intracavitary patients in this study but the study numbers were small and the light dose was relatively low at either 50 or 100 J/cm^2. Muller and Wilson[93,102,120] and Schmidt et al.[129] have also utilized the lipid filled inflatable-laser balloon adapter for intracavitary PDT to achieve uniform light distribution throughout the tumour cavity. These groups have used either laser fibres[93,102,120] providing single wavelength excitation of the PS or light emitting diodes (LED) emitting a broader spectrum of light around one of the absorption peaks of the PS[129] within an intracavitary balloon device.

Our concern with intracavitary illumination utilising balloon devices is that a small film of blood may develop between the balloons and the adjacent cavity wall during the illumination, thereby reducing light penetration locally, such that it would impair any PDT effect.

5.3. Intracavitary illumination with fibres

Intracavitary illumination with optical fibres involves the use of a light dispersing lipid solution to uniformly distribute the light within the resected tumour cavity. The solution also serves to keep the illuminated area at physiological temperatures and prevent any hyperthermic effect. Intracavitary photoactivation has been used by many investigators[94,95,99,118,119,112] with variations in the survival times of GBM patients. It is likely that there is a synergistic effect between hyperthermia and PDT, resulting in a greater tumour kill. However, in our series, we have attempted to negate a hyperthermia effect, in order to study the 'pure' effects of PDT on cerebral glioma. The varied survival response may be due to the different light doses administered to the patients ranging from 50 J/cm^2 to 240 J/cm^2. Light fluence and its distribution will also strongly depend on the optical properties of the tissue and the technique of illumination and therefore, suboptimal dosimetry may result in significant variations in treatment responses between patients.

6. PDT side effects

Cerebral oedema manifesting as swelling of the brain causing raised intracranial pressure has been reported as a complication of PDT[93,97,130] even though perioperative steroids have been used. However in our series cerebral oedema has usually been readily controlled with steroid therapy.[103] It is possible that in the RMH series,[95,103,119] the rigorous resection of tumour and consequently fewer residual cells undergoing necrosis following PDT result in less cellular toxic products released to produce acute cerebral oedema. Also, a more extensive resection would result in the presence of a larger cavity for any oedematous brain to expand into after the treatment. Skin photosensitization is also a problem for the porphyrin based PS. In general, patients stay sensitized for a period of up to 6–8 weeks

and are asked to remain out of direct sunlight for 3–4 weeks and then gradually increasing their exposure.

Glioma patients that have undergone additional adjuvant therapies such as chemotherapy and radiotherapy do not show any additional effects of either therapy as reported by Kostron et al.[118] and Kaye et al.[103,119]

7. PDT glioma clinical trials

Since 1980, over five hundred glioma patients have been treated globally with PDT primarily with a hematoporphyrin based PS such as HpD, Photofrin or Photosan (see Table 1). Many light sources and laser systems have been used as well as varying light doses to treat gliomas since the first patient in 1980. The variation in PS composition, laser or light systems used, light doses delivered and even the systems for grading gliomas, mean that the results are difficult to evaluate and compare.

We have treated over 350 patients with glioma utilizing PDT as an adjuvant therapy. In our study of patients resident in the State of Victoria[119] there was a median survival of approximately 14.3 months for primary GBM patients with 28% survival more than 24 months and 22% of patients surviving long term beyond 60 months (Fig. 1). This is encouraging given that the Central Brain Tumour Registry of the United States showed that greater than 90% of GBM patients were deceased at 2 years after initial diagnosis.[131] The results from this study were especially promising for recurrent GBM patients where 41% of these patients survived beyond 24 months and 37% beyond 36 months following repeat surgery (Fig. 2).

Kostron et al.[91] reported on 12 primary and 39 recurrent glioma patients who were treated with a variety of first generation PS such as HpD, Photofrin and Photosan. The median survival for the 12 primary patients was 19 months with the median time to recurrence from initial surgery 7 months and 9 months respectively when PDT was used. Muller and Wilson[93] reported a median survival of 9.2 months for recurrent patients after they were categorized

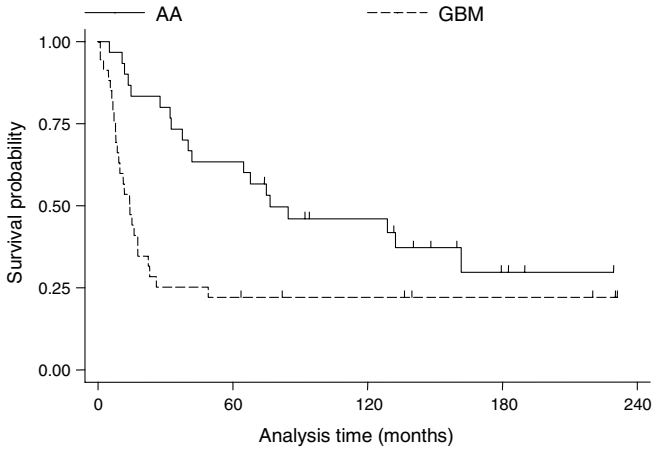

Fig. 1. Primary tumour: Kaplan Meier estimates of survival with photodynamic therapy from initial radiological diagnosis, by tumour grade.[119] AA = anaplasticastrocytoma; GBM = glioblastomamultiforme.

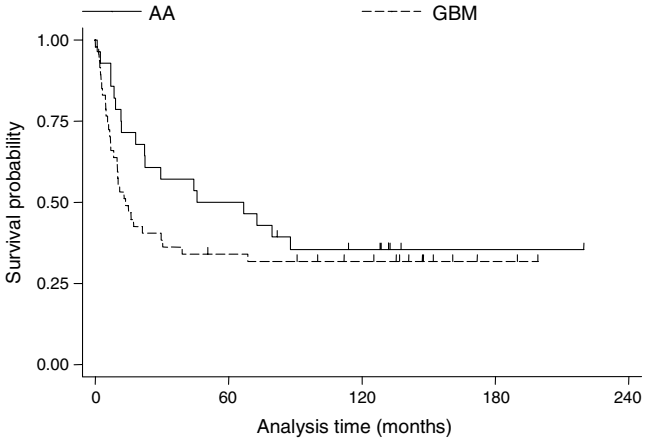

Fig. 2. Recurrent tumour: Kaplan Meier estimates of survival with photodynamic therapy from repeat surgery, by tumour grade.[119] AA = anaplasticastrocytoma; GBM = glioblastomamultiforme.

to light doses above 1700 J. Twenty-one percent of the primary tumour patients survived to 2 years compared to 16% of their recurrent patients. Kaneko et al.[132] treated 22 patients with a median survival of only 8 months. Age may also be an important prognostic factor in survival in patients with glioma and this was evident in our study.[119] Older age at diagnosis was generally associated with poorer prognosis.

A phase I trial conducted at the Royal Melbourne Hospital using a novel boronated porphyrin (BOPP) in the treatment of high grade glioma has shown encouraging survival particularly with recurrent glioblastoma patients with 56% of the patients surviving at least 12 months (median 11 months).[105] Our study[95] has shown that survival can also be linked to PS uptake. The level of HpD uptake was associated with better prognosis across the GBM and AA tumour grades with a stronger association present within the GBM group of patients. An increased local concentration of PS would result in more singlet oxygen also being available for destroying the tumour cells during PDT treatment. This relationship was not evident in a study by Kostron who used a variety of first generation PS including HpD, Photofrin and Photosan.[91] In their study, the porphyrin uptake in the GBM patients ranged from 1.46 to 4.0 μg/g compared to the 1.5 to 11.9 μg/g in our study as a result of using a 2.5 mg/kg dosing regime versus the 5 mg/kg dose in our study. A higher level of singlet oxygen being generated in the higher uptake patients may help account for the difference in survival. Also, as PS undergo photobleaching during PDT treatment, tumour sites with a lower concentration of PS may be more susceptible to photobleaching and therefore reducing the local phototoxic effect of the PDT treatment.

The area of light dosimetry is an important aspect of the PDT response. Underdosing of the total light dose may be the cause of many treatment failures and this may be inferred from the early studies as shown in Table 1. Lower light doses used in these early studies may explain why the median survival times are lower than those reported

by others.[119] The survival of both AA and GBM patients is increased when light doses above the study median of 230 J/cm^2 were used.

The clinical application of PDT for the treatment of gliomas is dependent on a variety of factors. Firstly, as we are generally using first generation PS, the design and manufacture of a water-soluble, non-toxic highly selective PS with excitation at a longer wavelength than the currently used 630 nm will be a major step for this type of therapy. The effect of a PS with greater selectivity was seen in our series.[95] GBM patients with a higher HpD uptake above the median level of 5 μg/g from this series survived longer than patients who had a level below 5 μg/g. It is expected that a higher concentration of PS in the tumour environment would increase the efficiency of PDT on the tumour through the increased generation of the cytotoxic singlet oxygen species. Laser light sources have progressed from the early days of the argon ion laser to the compact diode lasers which are in use today. A compact solid state laser which can be easily tuned to a variety of wavelengths or the two photon femtosecond lasers allowing greater tissue penetration would be advantageous.

As PDT is currently used as an adjuvant therapy to surgery, chemotherapy or radiotherapy, its coupling to an additional therapy may improve the overall treatment efficacy. An example of this is boron neutron capture therapy where the synthesis of a boronated porphyrin can be used as a dual sensitizer for PDT and neutron capture therapy.[104,105] Advances in the light delivery and dosimetry systems may also improve the delivery of light to the tumour site facilitating the PDT process.

8. Conclusion

In the last 25–30 years, thousands of patients have been treated with PDT for a variety of cancers.[133,134] The results from the series listed in this review indicate that PDT would seem to have real potential in neurosurgery for the treatment of gliomas as an adjuvant therapy. More laboratory research coupled with properly structured controlled trials investigating the effects of PDT are needed to properly demonstrate the effectiveness of PDT in the treatment of glioma patients as further success is currently limited by the availability of a small number of PS that are not ideal as well as less than optimal light and PS dosing regimes.

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