Novel Approaches for Efficient Delivery of Tyrosine Kinase Inhibitors

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Received, September 15, 2018; Revised October 25, 2018; Accepted, January 7, 2019; Published, January 9, 2018.

ABSTRACT - Epidermal growth factor receptors (EGFRs) have potential to be considered as therapeutic target for cancer treatment especially in cancer patients with overexpression of EGFR. Cetuximab as a first monoclonal antibody and Imatinib as the first small molecule tyrosine kinase inhibitor (SMTKI) were approved by FDA in 1998 and 2001. About 28 SMTKIs have been approved until 2015 and a large number of compound with kinase inhibitory activity are at the different phases of clinical trials. Although Kinase inhibitors target specific intracellular pathways, their tissue or cellular distribution are not specific. So treatment with these drugs causes serious dose dependent side effects. Targeted delivery of kinase inhibitors via dendrimers, polymeric nanoparticles, magnetic nanoparticles and lipid based delivery systems such as liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) can lead to reduction of side effects and improving therapeutic efficacy of the drugs in the target organs. Furthermore formulation of these drugs is challenged by their physicochemical properties such as solubility and dissolution rate. The main approaches in order to increase dissolution rate, are particle size reduction, self-emulsification, cyclodextrin complexation, crystal modification and amorphous solid dispersion. Synergistic therapeutic effect, decreased side effects and drug resistant, reduced cost and increased patient compliance are the advantages associated with using combination therapy especially in the treatment of cancer. Combination of TKIs with chemotherapeutic agents or biopharmaceuticals such as monoclonal antibodies and oligonucleotides and also combination of two TKIs within one formulation is possible by new targeting delivery systems. This article reviews the recent advances in the design and development of delivery systems for TKIs.

INTRODUCTION

Epidermal growth factor receptors (EGFRs) are cell membrane bound proteins which are belonging to human epidermal receptors (HERs) family. EGFRs are over expressed in various types of solid tumors which is responsible for pathogenesis, proliferation, invasion, angiogenesis and metastasis (1). These receptors are consisting of three regions: an extracellular ligand binding site; an intracellular domain with tyrosine kinase activity and regulatory functions; and a region that binds the receptor to the cell membrane (2-4). Inhibition of tyrosine kinase leads to apoptosis promotion, inhibition of angiogenesis and finally preventing excessive cell proliferation (5-7). Therapeutic response of cancer patients with overexpression EGFR to both chemotherapy and radiation therapy is poor (1). Therefore these receptors have potential to be considered as therapeutic targets (7). Concept of epidermal growth factor receptors inhibition was defined by introducing of Cetuximab as a monoclonal antibody in 1998 (8). It selectively binds to EGFR and competitively inhibits binding of epidermal growth factor to its receptor (9-10). Then Imatinib as the first small molecule tyrosine kinase inhibitor (SMTKI) was approved by FDA for treatment of chronic myeloid leukemia in 2001 (11). About 28 SMTKIs have been approved until 2015 and a large number of compound with kinase inhibitory activity are at the different phases of clinical trials (12). Although the vital role of SMTKIs is in the field of oncology, other indications of these compounds investigated and finally led to approval of Tofacitinib for rheumatoid arthritis and Nintedanib for pulmonary fibrosis (13-14). Even though kinase inhibitors are belonged to the type of drugs that target specific intracellular pathways, their tissue or cellular distribution are not specific.

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Thus treatment with these drugs causes serious dose dependent side effects. Targeted delivery of kinase inhibitors can lead to decrease side effects and increase the therapeutic efficacy of the drug in the target organ (15). Also improvement in the treatment of diseases can be achieved by pharmacokinetics alteration via increasing the circulation time of the drug. For instance the treatment of glioblastoma or other central nervous system disorders are limited by biological barriers such as blood brain barrier hence specific targeting may improve transport of kinase inhibitors over this barrier (16-17). A summary of investigated delivery systems for various TKIs are demonstrated in table 1. Another approach to improve therapeutic efficacy, reduce drug resistant and also decrease adverse effects in the field of oncology is combination therapy. Combination of TKIs with chemotherapeutic agents or biopharmaceuticals such as monoclonal antibodies and oligonucleotides and also combination of two TKIs within one formulation is possible by new targeting delivery systems (18-20). In this paper we review novel delivery systems which can be used as efficient delivery of TKIs.

NOVEL TARGETING DELIVERY OF TKIS

Targeting delivery of tyrosine kinase inhibitors are possible via various approaches such as dendrimers, polymeric nanoparticles, magnetic nanoparticles and lipid based delivery systems such as liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Methods of preparation, utilized In vivo tests and outcomes of various delivery systems for TKIs are shown in table 2.

Dendrimers

Dendrimers are branched mono-disperse spherical polymers. Dendrimers molecules consist of a group of atoms as the core and the branches of other atoms added to the core via the variety of chemical reactions. The core molecule reacts with reactive monomers via step by step controlled synthesis and different generation of dendrimers is produced in each step. Their suitable structures make them as suitable carriers in drug and gen delivery (21-23). Prolonged residence time of the drug in the blood circulatory system is the direct result of dendrimers pegylation by altering solubility, biodistribution and pharmacokinetics (24). Therefore pegylated 5ith generation (G5) Poly (propylene imine) dendrimers were synthesized as delivery systems for Imatinib. The aqueous solubility of Iimatinib was increased in these dendrimers based delivery systems (25). Cationic polyamidoamine (PAMAM) dendrimers have an ethylenediamine core and branches with terminal amino (-NH2) groups (26). Dolman et al developed a Sunitinib-dendrimer conjugate via the platinum linker for delivery of Sunatinib into the proximal tubular cells of kidney. They conjugated Sunitinib to the terminal amines of PAMAM-G3. They concluded that in vivo accumulation of this novel compound make it suitable as efficient dendrimer therapeutics for the treatment of renal disease (27).

Polymeric nanoparticles

The polymeric nanoparticles are prepared from biocompatible and biodegradable polymers with size ranged between 10 to 1000 nm. Drugs can be dissolved, entrapped, encapsulated or attached to a nanoparticles matrix. Nanospheres and nanocapsules are two types of nanoparticles which can be obtained depending on their preparation method (28). The most extensive pharmaceutical researches on the topic of nanoparticles have been focused in the area of oncology because nanocarriers can concentrate preferentially in tumor masses, inflammatory sites, and infectious sites by enhanced permeability and retention (EPR) effect on the vasculature.

Table1. A summary of investigated delivery systems for various TKIs

Drug	Delivery systems	References
Erlotinib	Polymeric nanoparticles, Galactosylated liposomes, Solid lipid nanoparticles, cyclodextrin nanosponge, Solid self-emulsifying systems	(33, 51, 57, 64, 79)
Imatinib	Dendrimer based delivery systems, Polymeric nanoparticles, Nanostructured lipid carriers	(25, 39, 58)
Sunitinib	Dendrimer based delivery systems	(27)
Apatinib	Pegylated polymeric nanoparticles, Pegylated cRGD liposomes	(38, 50)
Nilotinib	Solid dispersion	(73)

This effect is based on the fact that pathological vasculature, unlike vasculature of normal healthy tissues, is leaky. It means that large molecules and even small particles can penetrate and accumulate in the interstitial tumor space via this effect. Such accumulation is additionally facilitated by the virtual lack of a lymphatic system which is responsible for the drainage of macromolecules from normal tissues and increased production of a number of permeability mediators in many tumors. It has been reported that the effective pore size in the endothelial lining of the blood vessels in most peripheral human tumors ranges from 200 nm to 600 nm in diameter. Depending on the cutoff size of the leaky vasculature, passive targeting of nanoparticles to tumors is possible (29-32). PLGA nanoparticles containing Erlotinib hydrochloride were produced by Marslin et al. They found that these nanoparticles demonstrated less sub-acute toxicity than free drug in rats (33). In another study which was conducted by Barghi et al. Erlotinib loaded nanoparticles were prepared following synthesis of poly caprolactone-ethylene glycol- caprolactone (PCEC). Triblock PCEC copolymers were synthesized by ring opening polymerization method and then Erlotinib loaded PCEC nanoparticles were prepared via solvent displacement method. They concluded that the prepared PCEC nanoparticles might have the potential to be considered as delivery system for Erlotinib (34-36). Human serum albumin (HSA)-conjugated polyethylene glycol containing Apatinib for treatment of ocular diseases, including corneal neovascularization via suppressing angiogenesis was prepared by Lee et al. They demonstrated subconjunctival injection of these nanoparticles significantly reduced corneal neovascularization, whereas the injection of free Apatinib solution did not show this effect. The most limitation of free drug subconjunctival injection is the rapid clearance of these drugs from ocular tissue. Therefore sustained release of Apatinib from HSA-PEG nanoparticles can increase its therapeutic efficacy (37-38). Furthermore Imatinib mesylate-loaded polybutylcyanoacrylate nanoparticles were prepared and evaluated. Their high encapsulation efficiency (86%) and appropriate cytotoxicity profile make them as valuable system for delivery of Imatinib to leukemia cell line K562 (39).

Magnetic nanoparticles

Delivery of drugs to the target organ is possible via their incorporating in Magnetic nanoparticles. By using an external magnetic field, drugs are concentrated in target sites (40). In the study which was conducted by Xu et al. Erlotinib loaded multifunctional magnetic nanoparticles were prepared. Firstly multifunctional, carbon-coated, iron nanoparticles (C/Fe MNPs) were synthesized using the radio-frequency chemical vapor deposition method. Then erlotinib was incorporated onto the surface of C/Fe MNPs through the relatively simple noncovalent - stacking process. These nanoparticles show strong magnetic properties due to their atomic iron-core structures. The carbon shells are very stable and easy to bio-functionalize, making such nanoparticles very well dispersible in aqueous solutions, and thereby especially suitable for use in biological applications. (41).

Liposomes

Liposomes are artificial phospholipid vesicles without any toxic or antigenic reactions. Size of these vesicles which are biologically inert and completely biocompatible is in the range of 50 to 100 nm. Water-soluble drugs can be loaded into their inner aqueous compartment and water insoluble drugs can be incorporated into the hydrophobic compartment of their phospholipid bilayer (32). Liposomes can be passively accumulated in tumors through EPR effect (42). Nevertheless they eliminated from the body via rapid clearance by the reticuloendothelial system. Thus pegylated liposomes have been used in order to overcome this problem (43). Besides passive targeting mechanism, liposomes exhibit active targeting by adding various specific ligands such as antibodies and integrin ligands (44). Integrin αvβ3 is overexpressed in most tumors which are responsible for tumor angiogenesis, growth, and metastasis. One of the integrin ligands which recognized by Integrin αvβ3, is a tripeptide consisting of arginine–glycine–aspartic acid (RGD). Thus by modification of liposomes with RGD, active targeting of drugs to tumors is possible (45). Although Linear RGD peptides are active against several integrins but they don't show suitable selectivity profile. Cyclization of RGD peptides increases their binding affinity and selectivity (46-47). Therefore by synthesis of multiple cyclic RGD peptides, such as c(RGDfK), c(RGDyK), RGD4C and RGD10, affinity and selectivity of these ligands was improved (48-49). Pegylated Apatinib loaded cRGD liposomes were developed by Song et al. recently in order to passive and active targeting with long circulation time in the

body. They concluded that these modified Apatinib liposomes could be shown high efficacy in treatment of colon cancer (50). In another study galactosylated Erlotinib liposomes were developed for treatment of lung cancer by solvent evaporation method. Results demonstrated improvement of drug targeting and increasing relative bioavailability of Erlotinib from galactosylated liposomes were possible (51).

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)

SLNs are drug-delivery systems containing solid lipids which are dispersed in an aqueous medium. Fatty acids, steroids, waxes, monoglycerides, diglycerides and triglycerides are used as solid lipid in their structure (52). SLNs may be used for incorporating both hydrophilic and hydrophobic drugs (53). NLCs are composed of both solid and liquid lipids. Stability and loading capacity of drugs which is delivered by NLCs in comparison to drugs incorporated to SLNs is improved (54-56). Lipid based drug delivery systems including SLNs and NLCs have been used extensively for cancer treatment in recent years. For example in a study, Erlotinib loaded solid lipid nanoparticles were prepared and then spray dried by using mannitol as carrier in order to prepare dry powder inhaler (DPI). Therefore microparticles containing erlotinib SLN with appropriate flowability and aerodynamic properties for pulmonary delivery of erlotinib were prepared (57). Imatinib loaded NLCs was prepared via "hot homogenization followed by sonication using labrafi as liquid lipid and precirol as solid lipid by Gupta et al. Their In vitro and pharmacokinetic evaluation revealed that this lipid-based formulation might have the potential to be considered as efficient delivery system for Erlotinib (58).

SOLUBILITY MODIFICATION OF TKIS

Most of the drugs which belongs to TKIs are poor soluble; some of them with high permeability and others with low permeability. Hence, TKIs belong to class II or IV Biopharmaceutical Classification System (BCS). Class II and class IV (BCS) characterized by low solubility, high permeability and low solubility, low permeability respectively. Bioavailability of class II drugs are limited by dissolution rate but bioavailability of class IV drugs are dependent on both dissolution and permeability (59-60). Therefore, the most important strategy to improve bioavailability of the class II and IV is their dissolution enhancement. The main approaches in order to increase dissolution rate, are particle size reduction, self-emulsification, cyclodextrin complexation, crystal modification and amorphous solid dispersion (61-64).

Nanocrystal formation

The solubility of nanocrystals are appropriate due to their very high surface area and they can be incorporated into oral products by numerous methods of solidification such as spray drying(65), lyophilization (66), and electro-spraying (67). Physical and chemical stability of liquid nanosuspensions were improved by solidification methods. Erlotinib nanocrystals were produced for incorporating in solid dosage forms by Thakkar et al. Firstly they prepared erlotinib nanosuspension via nanoprecipitation technique followed by probe sonication. Methanol, ethanol, acetone, dichloromethane and ethyl acetate as solvent and Pluronic® F-127, Pluronic® F-68, SLS, and PVP K-30 as stabilizer were used in this study. Then nanosuspensions were solidified via both lyophilization and electro-spraying methods. Lyophilized powder had superior physicochemical properties in comparison to electrosprayed powders (68).

Solid dispersions

Another formulation development approach for solubility enhancement involves formation of amorphous form of drugs (69). Higher Gibbs free energy of amorphous drugs than crystalline drugs let them to have higher solubility (70). However amorphous materials are unstable (71). Therefore amorphous form of drugs is incorporated into polymer matrixes due to formation of solid dispersion (72). Nilotinib spray dried solid dispersion was developed by Herbrink et al (73). Nilotinib Hydrochloride is poorly soluble and also its permeability is low because of P-gp transporters which efflux Nilotinib out of cell; hence it belongs to (BCS) class IV (74). In this study various polymers such as Kollidon, Lutrol and Soluplus with different drug:polymer ratios were used. Among them, co-block polymer Soluplus with 1:7 (Nilotinib: Soluplus) ratio exhibited improved solubility which resulted in high bioavailability (73).

Solid self-emulsifying drug delivery systems

One of the approaches in order to increase dissolution rate, is developing self-Emulsifying drug delivery systems (SEDDS) (75). These systems are

containing oils, surfactants, co-surfactants and co-solvent which can be used in order to deliver lipophilic drugs. They spontaneously form oil-in water emulsions while exposed to aqueous medium (76). The most important problem related to the conventional SEDDS is their storage instability. Solidification of these delivery systems is the beneficial procedure to overcome this problem (77-78). In a study was performed by Truong et al. solid SEDDS formulations of Erlotinib were prepared by spray drying method (79). Erlotinib belongs to the (BCS) class II with low solubility and high permeability. Therefore rate limiting step for absorption of Erlotinib from oral solid dosage form is the dissolution phase (80-81). In a study was performed by Truong et al. the liquid SEDDS formulations were initially prepared by dissolving Erlotinib in mixtures of the various oil, surfactant, and co-surfactant at room temperature. Then, spray drying procedure were used in order to prepare solid SEDDS formulations. Dextran 40 and colloidal silica (Aerosil® 200) were chosen as the carriers for construction of solid SEDDS. Their results demonstrated that Erlotinib was in the amorphous state in solid SEDDS and exhibited faster dissolution rate than pure drug. Their pharmacokinetic studies in rats indicated that bioavailability of Erlotinib in these formulations was improved in comparison to pure drug (79).

Cyclodextrin complexation

Cyclodextrins are cyclic oligosaccharides containing six, seven, eight or nine glucose units. Cyclodextrins are water soluble because of their hydrophilic surface and they can form inclusion complexes with a various types of hydrophobic molecules due to their hydrophobic interior (63, 82-83). The cyclodextrin-based nanosponges are crosslinked polymeric systems composed of β - cyclodextrins with a high capacity to interact with small molecules in its matrix and a suitable crosslinker such as carbonyldiimidazole, pyromellitic dianhydride and diphenyl carbonate. Cyclodextrin-based nanosponges can form complexes with different types of lipophilic or hydrophilic molecules (84-85). For instance Erlotinib β cyclodextrin nanosponges were prepared using carbonyldiimidazole as crosslinker in order to enhance solubility and oral bioavailability of Erlotinib. Therefore solubility and oral bioavailability improvement of Erlotinib in these formulations may result in its reduction in dose and dose related side-effects (64).

DELIVERY SYSTEMS FOR COMBINATION THERAPY OF TKIS

Synergistic therapeutic effect, reduced side effects and drug resistance, reduced cost and increased patient compliance are the advantages associated with using combination therapy especially in the treatment of cancer (86-87). A clinical trial was performed by Lee et al. in order to evaluate efficacy of Afatinib and Nimotuzumab combination. Combination therapy showed therapeutic benefit in Non-small cell lung cancer (NSCLC) patients with acquired resistance to Gefitinib or Erlotinib (88). Effectiveness of Erlotinib and Bevacizumab; an antivascular endothelial growth factor (VEGF) antibody combination and also combination of Geftinib and Bevacizumab evaluated and the results showed promising effect for treatment of lung cancers patients with EGFR mutations (89-90). Moreover Triplet therapy with Afatinib, Cetuximab, and Bevacizumab demonstrated appropriate outcomes in the treatment of lung cancers patients with EGFR mutations (91). Lapatinib could sensitize human epidermal growth factor receptor-2 (HER-2) positive gastric cancer to Paclitaxel and exhibit synergetic effect with Paclitaxel in clinical trial (92). A novel micellar system by using poly ethylene glycol and poly lactic acid (PEG- PLA) diblock copolymers containing Lapatinib and Paclitaxel were prepared by Wei et al. They concluded that Lapatinib could extremely increase antineoplastic effect of paclitaxel via co-delivery of Lapatinib and Paclitaxel by this novel micellar system (93). For co-delivery of Lapatinib and Paclitaxel, additional novel system was described by Hu et al. They incorporated Paclitaxel nanoparticles and Lapatinib microparticles into a thermosensitive hydrogel for peritumoral injection (94). Furthermore Co-delivery of Lapatinib and Paclitaxel through liposomal formulation was described by Ravar et al (95). Folate receptor targeted pH-sensitive pegylated liposomes containing both Imatinib and Doxorubicin which can be delivered two drugs in tumor acidic environment is a novel approach to improve chemotherapeutic efficacy against MDR tumors (96). Furthermore, nanostructured lipid carriers (NLCs) containing Curcumin and Imatinib were prepared and conjugated to high-density lipoprotein (HDL) to target scavenger receptor type B-1 which is expressed by lymphoma cells.

Table2. An overview of preparation methods, utilized In vivo tests and outcomes of various delivery systems for TKIs

Delivery system	Drug	Method	In vivo tests	Outcome	Reference
Dendrimer based delivery systems	Imatinib	Dialysis	-	Aqueous solubility enhancement	(25)
Dendrimer based delivery systems	Sunitinib	Conjugation	renal accumulation assay	In vitro internalization and in vivo kidney accumulation	(27)
PLGA nanoparticles	Erlotinib	Sonication-solvent evaporation	toxicity test	Less subacute toxicity	(33)
Pegylated HAS polymeric nanoparticles	Apatinib	Thin film rehydration	corneal distribution	Decreasing clearance of drug from ocular tissue	(38)
Polybutylcyanoacrylate nanoparticles	Imatinib	Miniemulsion polymerization	-	High encapsulation efficiency and appropriate cytotoxicity profile	(39)
Pegylated cRGD liposomes	Apatinib	Thin-film hydration	antitumor efficacy test	High cellular uptake, improvement in biodistribution and tumor selectivity	(50)
Galactosylated liposomes	Erlotinib	Solvent evaporation method	Biodistribution studies	Improvement of body distribution and relative bioavailability enhancement	(51)
Nanostructured lipid carriers	Imatinib	Hot homogenization	pharmacokinetic studies	Bioavailability enhancement	(58)
Erlotinib Nanocrystals	Erlotinib	Nanoprecipitation followed by Lyophilization or electrospraying	-	Solubility enhancement	(68)
Solid dispersion	Nilotinib	Spray drying	-	Solubility enhancement	(73)
Solid self-emulsifying systems	Erlotinib	Spray drying	pharmacokinetic study	Solubility and bioavailability enhancement	(79)
Erlotinib cyclodextrin nanosponge	Erlotinib	Complexation and freeze drying	pharmacokinetic study	Solubility and oral bioavailability enhancement	(64)

Their findings suggested that NLCs delivery system containing curcumin and Imatinib can be more beneficial than Imatinib alone in the treatment of B cell lymphoma (97). Using TKIs in combination with Short interfering RNA (siRNA) is additional strategy for efficient treatment of cancers. Various

siRNA molecules including anti-drug resistance siRNA, EGFR siRNA and VEGF siRNA can be used with TKIS simultaneously to overcome drug resistant, prevent angiogenesis and improve therapeutic efficacy of TKIs (18, 98-100). For instance the porous gelatin triblock nanoparticles containing Geftinib and Cetuximab- siRNA conjugate was synthesized. Initially gelatin nanoparticles were prepared via two steps desolvation process. Geftinib was incorporated to nanoparticles prior the second desolvation step. The carboxyl groups on the surface of the Geftinib loading nanoparticles activated and reacted with Cetuximab in order to preparation of Cetuximab conjugated nanoparticles and finally conjugation of Cetuximab to siRNA was performed (98). The nucleic acid based drugs such as siRNA have hydrophilic structure and are negatively charged. Therefore delivery of these drugs inside the cells is a complicated process. Instability of siRNA due to enzymatic degradation is additional drawback (101). It has demonstrated that porous gelatin triblock nanoparticles containing Geftinib and Cetuximab-siRNA conjugate can efficiently deliver siRNA to cytoplasm of KRAS mutant H23 non-small cell lung cancer (NSCLC) cells (98).

CONCLUSION

Drugs which belongs to TKIs are poor soluble; some of them with high permeability and others with low permeability. Hence, TKIs belong to class II or IV Biopharmaceutical Classification System (BCS). Formulations of these drugs are considered challenging because of their physicochemical properties such as solubility, dissolution rate and permeability. Therefore, various approaches are being investigated to design and develop novel and efficient delivery systems for TKIs in recent years. The difficulties confronted by the conventional formulations such as dose dependent side effects, variable bioavailability and non-specific tissue distribution have been addressed by utilizing novel strategies particularly nanostructured systems. Drug resistance caused by efflux mechanism, have been explored to minimize via combination of TKIs with other drugs using Co-delivery of TKIs with chemotherapeutic agents or biopharmaceuticals such as monoclonal antibodies and oligonucleotides. In this regard, combination of two TKIs is also found favorable as included in new targeting delivery systems like NLCs, pegylated liposomes and nanoparticles. Although considerable amount of delivery systems for TKIs are under investigations, but further in vivo studies are essential to confirm therapeutic benefits of these formulations compared to free drugs.

CONFLICT OF INTEREST

The authors report no conflict of interest.

ABBREVIATIONS

EGFRs: Epidermal growth factor receptors; HERs: Human epidermal receptors; SMTKI: Small molecule tyrosine kinase inhibitor; TKI: Tyrosine kinase inhibitor; EPR: Enhanced permeability and retention; SLN: Solid lipid nanoparticle; NLC: Nanostructured lipid carrier; PAMAM: Polyamidoamine; PCEC: Poly caprolactone-ethylene glycol- caprolactone; HSA: Human serum albumin; RGD: Arginine–glycine–aspartic acid; BCS: Biopharmaceutical Classification System; SEDDS: self-Emulsifying drug delivery systems

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