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Systemic Management of Advanced Hepatocellular Carcinoma Patients: The Role of Multi-Targeted Anti-Angiogenic Inhibitors

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1. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide resulting in between 250,000 to one million deaths per annum. It carries dismal prognosis and the number death is close to the incidence of disease owing to the aggressive nature of this tumor. The incidence of HCC is highest in China, eastern Asia, and Saharan African. The main etiology of HCC in these regions is chronic hepatitis B viral infection. In most Western countries, HCC is mainly related to hepatitis C infection and alcoholic liver disease. Nonalcoholic steato-hepatitis and exposure to aflatoxins are also known risk factors for development of HCC.

Advanced non-resectable HCC has a median survival of only 6 months [1]. Traditional cytotoxic chemotherapy has not been found to be effective in prolonging overall survival and is associated with significant hematological toxicities. The use of systemic chemotherapy is also limited by liver cirrhosis which often coexists in these patients.

2. Molecular biology and mechanism of HCC

Pathogenesis of HCC is a complex process. HCC is believed to be related to genetic alterations caused by chronic liver injury and inflammation. Cytokines release induced by death of hepatocytes, fibrogenesis, and liver cirrhosis are the early events marking hepatocarcinogenesis. Occasionally, however, HCC can arise in liver without evidence of chronic cirrhosis. Chronic infections with hepatitis B or C viruses are 2 important etiologies in development of this tumor. Integration of viral DNA in the human genome can potentially induce chromosomal instability, activate oncogenes or deactivate tumor-suppressor genes, promoting cancer formation. Known examples of mutations in the tumor suppressor genes or proto-oncogenes in HCC include p53, p73, APC, Rb, c-myc and cycline D1 [2]. Various viral proteins, such as HBs or preS in hepatitis B and core protein in HCV, have been linked to activation of transcription and cellular proliferation, although the exact mechanism is not known.

Cytogenic studies have shown chromosomal amplification or deletions are common in HCC. HCC is associated with high prevalent amplifications in 1q, 6p, 9q, 11q (contains areas encoding cyclin D1), 17q, and 20q [2, 3], and high prevalent deletions in 4q, 6p (contains

areas encoding VEGFA), 8p, 13q, 16q, and 17p [3]. Increase in tolemerase activity leading to telomere shortening and genomic instability, was also observed in nearly 90% of HCC [4]. The significance of these chromosomal alteration remains to be elucidated.

The advance of microarray in the last 2 decades have revolutionized oncological studies and shed light on the molecular mechanisms behind development of cancer. In many tumors, molecular studies successfully identified specific genes that drive the growth of malignancies, leading to development of targeted therapies for each tumor subtypes. For instance, imatinib was designed to block the tyrosine kinase activity associated with the kinase fusion protein BCR-ABL in chronic myeloid leukemia and became the standard of care for this tumor. Gefitinib and erlotinib targeting the tyrosine kinase activation caused by mutated EGFR in adenocarcinoma of lung, and significantly prolonged the life expectancy of patients carrying this genetic abnormality. However such pattern of oncogene addiction has not been identified in HCC. Today, a large body of knowledge have been accumulated to stratify specific gene expressions involved in various stages of HCC tumorgenesis [5]. For instance, early HCC development is marked by down-regulation of Toll-like receptor pathway, Jak/STAT pathway, TGF pathway, and the insulin-signaling pathway, with up-regulation of Wnt signaling pathway. Poorly differentiated HCC is characterized by decreased level of apoptosis-related proteins compared with well differentiated counterpart [6]. Furthermore, many scientists have demonstrated that HCC can be divided into prognostic significant subgroups based on gene signatures [7-11]. Although there is yet consensus on genetic classification of HCC, these data suggested HCC is a group of heterogeneous tumors each with distinct characteristics. This knowledge can path the future development of personalized medicine in treatment of HCC.

While our knowledge on genetic features of HCC continue to expand, much research focus on factors that govern more universal processes such as tumor cells proliferation, neovascularization, tumor invasion, and metastasis. Today, growth of HCC is considered as a result of dysregulation of pleiotropic growth factor signaling [12]. Implicated pathways include insulin-like growth factor/IGF-1 receptor (IGF/IGF-1R), hepatocyte growth factor (HGF/c-MET), stem cell growth factor receptor (c-kit), Wingless (Wnt/β-catenin/FZD), transforming growth factor β (TGFβ/TβR), epidermal growth factor/EGF receptor (EGF/EGFR), and many growth factor regulated angiogenic signaling such as fibroblast growth factor/FGF receptor (FGF/FGFR), platelet growth factor/PDGF receptor (PDGF/PDGFR), and vascular endothelial growth factor/VEGF receptor (VEGF/VEGFR). Activation by ligand binding on the extracellular portion of these transmembrane receptors results in phosphorylation of cytoplastic components, triggering downstream signaling cascades. These pathways are multifunctional and crosstalk to each other. The RAF/MEK/ERK pathway and phosphatidylinositol-3 kinase (P13K)/AKT/mammalian target of rapamycin (mTOR) pathway are some of the major intracellular cascades implicated in HCC.

3. Anti-angiogenic therapy

HCC is a characterized by its high vascularity and anti-angiogenesis becomes an intense area of study in the quest of new therapy for HCC. Angiogenesis plays a pivotal role in the growth to solid tumor. It is a complex multi-step process mediated by various proangiogenic growth factors such as BEFG, FGFs, TGFβ, interleukin-8 (IL8),

metalloproteinase-2 (MMP-2), angiopoietin (Ang), and PDGF. Genetic changes in tumor cells and hypoxia induced by rapid tumor growth could lead to increased secretion of these mediators, which promote migration, proliferation and survival of endothelial cells, as well as growth of stromal cells and extracellular matrix favoring these processes.

3.1 Sorafenib

Sorafenib (Bayer 43-9006; Nexavar) is a multikinase inhibitor of the VEGR-2, VEGFR-3, and PDGF receptor β, and blocks cellular proliferation mediated by the Raf/MAPK/ERK signaling pathway [13]. Two Phase III randomized placebo-controlled trails, the SHARP trial and the Asian-Pacific trial, have shown overall survival benefit using single agent sorafenib as first line treatment in advanced HCC [14, 15]. The SHARP trial contains mainly Westerners, whose etiology factors were predominantly HCV infection and alcoholic liver cirrhosis. It demonstrated sorafenib led to an improvement of median time to progression (TTP) from 2.8 to 5.5 months and overall survival (OS) from 7.9 to 10.7 months, when compared with the placebo group. The Asian-Pacific trial, where most subjects were Orientals, also found sorafenib improved median TTP from 1.4 to 2.8 months and OS from 4.2 to 6.5 months when compared with the placebo group. Based on these 2 independent studies, sorafenib become the first systemic treatment approved by the U.S. Food and Drug Administration (FDA) and many regulatory authorities worldwide for first line management of advanced HCC. It should be noted that, however, the absolute benefit of sorafenib in HCC remains modest. In both studies the OS improvement was between 2.3 to 2.8 months. The overall response rate was 24% in the Western study and 57% in the Asia-Pacific study, but most patients had stable disease and only 3% had partial response. Furthermore, over 95% of subjects in these 2 studies had Child-Pugh class A liver function, rendering the effect in those with poorer liver function controversial. Child-Pugh B or C liver cirrhosis commonly coexist in patients with HCC. A number of small retrospective series showed patients with Child-Pugh B liver function were more likely to have hyperbilirubinemia, encephalopathy, worsening of ascites, and shorter survival when given sorafenib [16-18]. Since patients with poor liver function would naturally have more of these complications and shorter survival, the safety and survival benefit of sorafenib in these patients is not known. A recently published abstract of the GIDEON study probably provides more insight on this issue. It is so far the largest prospective non-interventional study of sorafenib involving over 3000 patients with unresectable HCC. Patients were stratified according to different Child-Pugh status, with the safety and outcome of sorafenib treatment evaluated [19]. Interim analysis showed Child-Pugh B patients, compared with Child-Pugh A patients, did not have a higher incidence of drug-related adverse events (AEs), but had a higher incidence of liver-associated AEs. Kaplan Meier estimate showed similar TTP between 2 groups, and an obviously worse OS in patients with Child-Pugh B or C liver cirrhosis. Most deaths were due to HCC or underlying liver disorders and the differences in patient outcomes across Child-Pugh groups appeared to be attributed by differences in prognosis.

Combination therapy has been a common approach in cancer treatment. By acting on multiple sites of the cell proliferation pathways, there are potential for enhanced efficacy by synergistic effect, reducing the emergence of resistance clones, or minimizing the accumulated toxicities of high dose therapy.

In an attempt to enhance the effect of sorafenib, many clinical trials are undergoing to evaluate the addition of other biological agents to this drug. For example, SEARCH is a Phase III randomized placebo controlled, double blind trial of sorafenib plus erlotinib versus sorafenib plus placebo as first line systemic treatment for hepatocellular carcinoma.

Sorafenib has been combined with a number of chemotherapy. Abou-Alfa's team has published a double-blinded randomized phase II trial comparing doxorubicin with or without sorafenib. Doxorubicin was extensively studied in treatment of advanced HCC in the pre-sorafenib era. It showed minimal efficacy with significant toxicities. In this phase II study, combination sorafenib and doxorubicin showed some activity but only gave a 4% response rate, and the additional effect of chemotherapy was questionable since this study used doxorubicin as the control arm [20].

3.2 Bevacizumab

HCC is a highly vascularized tumor and it correlates with high level of VEGF expression [21], which is thought to be the most important proangiogenic growth factors. Bevacizumab is a humanized recombinant monoclonal antibiody against VEGF with high affinity [22] and has been shown to have efficacy in many solid tumors. Bevacizumab as a single agent has been shown to have activity in advanced HCC. In Siegel's Phase II study which enrolled 46 patients with HCC, bevacizumab (5 mg/kg or 10 mg/kg every 2 weeks) had a response rate of 13%, gave a PFS of 6.9 months and median OS of 12.4 months [23]. However, the use of this drug is complicated by significant hemorrhage in 11% and thrombosis in 6% of subjects. Interestingly, when bevacizumab (10 mg/kg every 2 weeks) was combined with chemotherapy gencitabine and oxaliplatin, the combination achieved an apparently higher RR of 20%, but yielded a median PFS and medial OS of only 5.3 months and 9.6 months respectively with major complications being leucopenia, transaminitis, hypertension and fatigue [24]. As chemotherapy appears to have limited role in the development of systemic treatment of HCC, the M.D. Anderson group brought forward the concept of combining bevacizumab with another biological agent. In their Phase II trial using bevacizumab with erlotinib which involved 57 patients [25], the combination gave a median PFS of 7.9 months and medial OS of 12.8 months. It is worth noting that 6 patients in this trial terminated treatment due to toxicities, but there were an impressive stable disease (SD) rate of 62% and partial response (PR) rate of 28%. This study also included both Child-Pugh A and Child-Pugh B patients although the proportion was not mentioned in the abstract. Meanwhile the same research group is exploring the effect of this drug combination compared with sorafenib as first line treatment in advanced HCC in a Phase II trial. In summary, early clinical trials showed that bevacizumab has some activity in HCC, but efficacy and safety of this drug needs to be clarified as it can potentially be associated with major complication such as thrombosis, hemorrhage and even death.

3.3 Sunitinib

The VEGF family is the most important proangiogenic mechanism known today. VEGF binds to cell surface receptors VEGFR-1, 2, and 3 on endothelial cells. Among these 3 receptors, VEGFR-2 is the primary tyrosine kinase receptor mediating the VEGF signaling. Sunitinib is another anti-angiogenic agent with potent anti-VEGF-2 activity. The concentration required to produce 50% inhibition (IC_{50}) of human VEGFR-2 kinase activity

is 0.009 μM compared with 0.09 μM for sorafenib [13, 26]. It is also an oral multi-targeted tyrosine kinase inhibitor with overlapping TKI activities with those of sorafenib, including VEGF receptors, RET kinases, PDGFR-α and β, c-Kit, Flt-3 and colony-stimulating factor receptor type 1 [26]. It was first approved for treatment of advanced renal cell carcinoma (RCC) [27], which is a highly vascularized tumor also resistant to traditional chemotherapy. In RCC, sunitinib and sorafenib demonstrated similar efficacy, thus it was suggested that they might also have comparable effect in advanced HCC. The use of single agent sunitinib as first line treatment in advanced HCC has been tested in a number of Phase II trials (see Table 1 for details) [28-30]. In these trials, sunitinib was given at 37.5 mg daily or 50 mg daily for 4 weeks out of a 6-week cycle, or continuously at 37.5 mg daily. The RR was relative low, with medial PFS between 2.8-5.3 months, and medial OS between 8 to 9.8 months. These data showed preliminarily encouraging survival time approximate those of sorafenib. Nevertheless, use of sunitnib in HCC requires vigorous testing in randomized controlled trial. Cheng et al. released their early Phase III data comparing sunitinib and sorafenib as first line treatment in an abstract form recently [31]. In their open-label trial involving over 1000 Child-Pugh A patients with advanced HCC, patients were randomized 1:1 to receive sunitinib 37.5 mg daily or sorafenib 400 mg BID. The primary end point was OS and secondary endpoint was PFS, time to progression (TTP) and safety. The trial was terminated prematurely, as interim analysis showed sunitinib had significantly shorter OS of 8.1 months compared with 10.0 months of sorafenib (p=0.019). There was no difference in PFS and TTP between 2 groups. Serious adverse events (AEs) in sunitnib and sorafenib groups were found in 44% and 36% of patients, and grade 5 AEs in 18% and 16% of patients respectively. Thus sunitinib failed its primary OS endpoint and was associated with more significant toxicities. Worth noting is that in this study, there was no OS difference between 2 groups among hepatitis B carriers. Formal report of toxicity profile is pending. These results did not support using sunitib as first line treatment in advanced HCC and sorafenib remains the standard choice. Use of sunitnib as second line treatment after sorafenib failure has also been reported by Yau et al. In this Phase II study which enrolled 35 patients, the RR was 6%, TTP was 2.9 months and OS was 5.2 months [32]. More clinical data is needed to elucidate the role of this TKI in treatment of advanced HCC.

3.4 Brivanib

Besides VEGF, the fibroblast growth factor (FGF) pathway is another key driver of angiogenesis. FGF is a potent angiogenic growth factor which stimulates induction and migration of endothelial cell precursors during vascular development [33]. It is also secreted by HCC and contributes to tumor growth [34]. Experiences from other cancers showed the expression of FGF and other angiogenic factors were upregulated upon anti-VEGF treatment, suggesting FGF pathway is one of the alternate escape mechanisms that contributes to resistance or failure of anti-VEGF treatment [35]. Brivanib (BMS-582664) is a novel TKI of both VEGF and Basic FGF (bFGF). In a Phase II open-label study of brivanib as first line treatment of unresectable HCC involving 55 patients, brivanib achieved a median PFS of 2.7 months and median OS of 10 months. Stable disease, partial response, and complete response were found in 22, 3, and 1 patients respectively [36]. Common adverse events included fatigue, hypertension and diarrhea. In view of shown activity and manageable toxicity profile, brivanib has been carried on to a Phase III multi-center double-blinded randomized controlled trial (BRISK FL study) which compares this drug with sorafenib as first line treatment of HCC. This trial has completed recruitment in July 2011

and data collection is underway. The same group of researchers who performed the Phase II brivanib trial also tested the efficacy of this drug in patients who failed prior antiangiogenic therapy. They recruited 22 such patients; of the 19 patients who were assessed for efficacy, 58% had stable disease. Alpha fetoprotein reduction of more than half was also found in 43% of patients [37]. This VEGF / FGF dual targeting agent can potentially become a new anti-angiogenic therapy in advanced HCC.

3.5 Pazopanib

Pazopanib (GW786034) is multi-targeted TKI of VEGFR1-3, PDGFR-α and β, and c-kit [38]. It shares with sunitinib and sorafenib similar preclinical activity in various xenograft tumors models including RCC, thyroid cancer, pancreatic cancer, and HCC [39]. Since it has no significant in vitro effect in proliferation of most tumor cell lines, it is believed its anti-tumor property owes to its anti-angiogenic activity. Clinically pazopanib has been approved by the U.S. FDA for treatment of advanced RCC [40] and has been shown to have promising activity in thyroid cancer [41] and urothelial cancer. Its use in HCC is still under preliminary research. Our group has recently published a Phase I tudy evaluating the early efficacy and pharmacological properties of pazopanib in HCC patients [42]. In this study of 28 patients, the maximum tolerated dose was 600 mg daily. The most common adverse events were diarrhea, skin hypopigmentation, and AST elevation. Grade 3 dose-limiting toxicities were observed in only 2 patients at the 800 mg dose level. Furthermore, 73% of patients responded with either partial response or stable disease. These results suggested pazopanib has acceptable toxicity and can potentially be a candidate for treatment of advanced HCC.

3.6 Other anti-angiogenic agents

Linifanib (ABT-869) is a novel and potent selective inhibitor of the EGF and PDGF families of RTKs. In a Phase II open-label trial, 44 Child-Pugh A or B patients with unresectable HCC were given linifanib at 0.25 mg/kg daily and 0.25 mg/kg alternate day respectively [43]. The overall response rate was 6.8%. For Child-Pugh A patients, median TTP was 5.4 months and median OS was 9.7 months. The most common grade 3 or 4 adverse events were hypertension and fatigue. A Phase III trial comparing linifanib with sorafenib is undergoing.

TSU-68 is another multi-targeted TKI with activity against VEGFR, PDGFR, and FGFR. In a Phase I/II trial, Kanai et al. reported an overall response rate of 51% with 2.9% complete response, 5.7% partial response and 42.8% stable disease. The median TTP was 2.1 months and median OS was 13.1 months [44]. Adverse events include diarrhea, malaise, and ALT / AST elevation, and were similar to other TKIs. This drug showed preliminary efficacy with acceptable safety profile.

Cediranib (AZD2171) is another investigational TKI activity against pan-VEGFR, PDGFR, c-kit an FLT-4 pathways. Recently published Phase II data suggested cediranib at 45 mg daily bared significant toxicity and did not show clinical response [45].

Axitinib (AG013736) is a multi-targated TKI with activity against VEGFR1-3, PDGFR and c-kit. This drug has encouraging survival data as both first and second line treatment in advanced RCC, and has shown promising activity in thyroid cancer [46, 47]. Phase II/III trials testing this drug in HCC is under planning.

The hepatocyte growth factor (HGF) and its receptor called mesenchymal epithelial transition factor (c-MET) is another potential target for treatment of HCC. The HGF/c-MET is involved in growth of hepatocytes [48]. The c-MET mediates cell growth, survival, motility and morphogeneis during early development of liver, as well as repair and regeneration in liver injury [49]. Foretinib (GSK1363089) is a novel receptor TKI targeting c-MET and VEGFR2/KDR in a Phase 1-2 clinical trial for systemic treatment of HCC.

4. Resistance to antiangogenic therapy

The mechanism underlying resistance to antiangiogenic treatment in HCC is still poorly understood. The proposed mechanisms include:

4.1 Redundancy of angiogenic signaling pathways

Tumour dependence on pro-angiogenic factors may be altered after the treatment with sorafenib [50]. The vascular remodeling that due to pericytic over-coverage renders the neovasculature less responsive to VEGF for growth dependence effectively circumventing a blocked signaling pathway with greater dependence on other alternate mechanisms [51].

4.2 Resistance occur at the tumour endothelial cell level

Published evidence has shown that tumour endothelial cells may harbor unstable genome [52]. These aberrant genomes may lead to an increase in genetic alterations and result in mutations in the endothelial cells. Thus, the mutated endothelial cells may acquire resistance to molecularly targeted therapy.

4.3 Increase the biological aggressiveness of the tumour following antiangioneic use

It has been shown that the inhibition of VEGF receptors may result in an increased propensity for metastatic dissemination as the hypoxic microenvironment associated with the sorafenib use selects for highly aggressive, invasive tumour cells [53, 54]

4.4 Splitting of pre-existing vasculature

Antiangiogenic agents inhibit sprouting angiogensis which heavily relies on the need for endothelial cell proliferation and migration. Tumour cells can potentially evade these pruning effects by the splitting of pre-existing vasculature into new blood vessels without a need for VEGF expression and endothelial cell proliferation[55] or form blood vessels without the need for endothelial cell proliferation [56].

4.5 Increase in the expression of the resistance efflux proteins

Resistance efflux proteins are members of the ATP binding cassette transporters, especially multidrug resistance protein 2(MRP2) may partly account for the development of sorafenib resistance. In vitro experiment performed by Shibayama et al. demonstrated that sorafenib is a substrate for MRP2 and thus MRP2 may implicate in the development of drug resistance to Sorafenib [57].

4.6 Presence of cancer stem cell

Cancer stem cells are typified by a capacity for self-renewal, relative quiescence and the ability to differentiate. Evidence has suggested that CSCs are involved in carcinogenesis, tumour invasion and metastases, and resistance to various forms of therapies, including chemotherapy[58].

5. Conclusion

The development of sorafenib marked an important milestone in the systemic treatment of advanced HCC. This drug remains the only approved targeted therapy shown to have survival advance in randomized controlled studies. Hepatocarcinogenesis is a complex process involving multiple growth factor systems which interact with each other. Early clinial trials suggested that agents with single-target activity probably cannot block HCC growth and multi-targeted therapies might be the trend for future drug development. As HCC in different stages demonstrated different molecular characteristics, and knowledge on molecular subgroups of HCC is expanding, we see the vast varieties of potential for development of HCC treatment.

Agents	Study	n	Response rate (%)	Median PFS (months)	Median OS (months)
Sorafenib					
Sorafenib vs. placebo	SHARP	602	24.4	5.5	10.7
Sorafenib vs. placebo	Asia-Pacific	226	57.3	5.5	6.5
Sorafenib + erlotinib Vs Sorafenib + placebo	SEARCH	Ongoing			
Bevacizumab					
Bevacizumab	Siegel 2008	46	13	6.9	12.4
Bevacizumab+gemcitabine & oxaliplatin	Zhu 2006	33	20 (SD 27%)	5.3	9.6
Bevacizumab+erlotinib	Kaseb	57	(SD 62%, PR 28%)	7.9	12.8
Sunitinib					
Sunitinib (37.5mg daily 4/6 weeks)	Zhu [28]	34	2.9	3.9	9.8
Sunitinib (50mg daily 4/6 weeks)	Faivre [29]	37	2.7%	5.3	8
Sunitinib (37.5mg daily continuous)	Koeberle [30]	45		2.8	9.3
Sunitinib vs. sorafenib	Cheng 2011	1073	Not a/v	3.6 vs. 2.9	8.1 vs. 10.0 ($p < 0.01$)
Brivanib					
Brivanib (800 mg daily)	Park 2011	55	47%	2.7	10
Brivanib vs. sorafenib	BRISK FL	Ongoing			

Table 1. First line trials for major antiangiogenic agents (shaded trials indicate Phase III studies)

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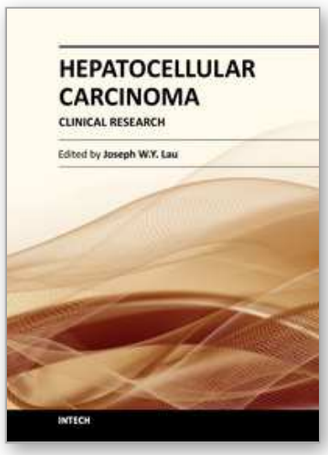
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This book covers the clinical aspects of hepatocellular carcinoma. This book is a compendium of papers written by experts from different parts of the world to present the most up-to-date knowledge on the clinical aspects of hepatocellular carcinoma. This book is divided into three sections: (I) Diagnosis / Differential Diagnosis; (II) Surgical Treatment; (III) Non-surgical Treatment. There are 19 chapters covering topics from novel diagnostic methods to hepatic lesions mimicking hepatocellular carcinoma, from laparoscopic liver resection to major hepatectomy without allogeneic blood transfusion, from molecular targeted therapy to transarterial radioembolization, and from local ablative therapy to regional therapy. This volume is an important contribution to the clinical management of patients with hepatocellular carcinoma. The intended readers of this book are clinicians who are interested in hepatocellular carcinoma, including hepatologists, liver surgeons, interventional and diagnostic radiologists, pathologists and epidemiologists. General surgeons, general physicians, trainees, hospital administrators, and instruments and drug manufacturers will also find this book useful as a reference.

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