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MINIREVIEWS

Current systemic treatment of hepatocellular carcinoma: A review of the literature

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common form of human cancer worldwide and the third most common cause of cancer-related deaths. The strategies of various treatments for HCC depend on the stage of tumor, the status of patient's performance and the reserved hepatic function. The Barcelona Clinic Liver Cancer (BCLC) staging system is currently used most for patients with HCC. For example, for patients with BCLC stage 0 (very early stage) and stage A (early stage) HCC, the curable treatment modalities, including resection, transplantation and radiofrequency ablation, are taken into consideration. If the patients are in BCLC stage B (intermediate stage) and stage C (advanced stage) HCC, they may need the palliative transarterial chemoembolization and even the target medication of sorafenib. In addition, symptomatic treatment is always recommended for patients with BCLC stage D (end stage) HCC. In this review, we will attempt to summarize the historical perspective and the current developments of systemic therapies in BCLC stage B and C in HCC.

Key words: Hepatocellular carcinoma; Transarterial chemoembolization; Sorafenib; Systemic treatment; Molecular target therapy

Core tip: Sorafenib is a multi-targeted tyrosine kinase

inhibitor that was the first systemic therapy in the world to improve the survival rate of patients with advanced hepatocellular carcinoma (HCC) in a phase Ⅲ trial. However, the overall outcomes are sometimes unsatisfactory and there is a need for second line therapies in patients with advanced HCC who still progress after the use of sorafenib. Novel systemic approaches are needed in advanced HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary cancer of the liver with a rate of occurrence approximately up to 90%. Clinically, HCC is the fifth most common form of cancer worldwide and the third most common cause of cancer-related deaths[1]. It is usually diagnosed as the advanced stage of the hepatic tumor and the median survival rate is poor (6-20 mo) when found[2]. The incidence and distribution of HCC varies widely among geographical locations and races in the world. For example, the incidence of HCC is highest in Asia and Africa. Now most doctors believe that the potential reason for the higher incidence rates of HCC is the prevalence of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) which strongly predisposes to the development of chronic liver disease, liver cirrhosis and subsequently HCC[3]. In 1988, one large prospective HBV study in Taiwan robustly demonstrated that HBV is the primary cause of the high HCC incidence rate in regions of high HBV prevalence[4]. In Taiwan, nearly 5000 patients die from HCC every year. Although the newer treatment modalities have become more multivariate in recent years, the survival rates of patients with advanced HCC has still not significantly improved. The one year survival rate of treated patients with advanced HCC was around 25% in 1993 and 30% in 2003[5]. Until recently, there was no remarkable and effective medical therapy for patients with advanced HCC. To the best of our knowledge, HCC is a more aggressive tumor and the decision regarding therapeutic options often depends on the stage of this cancer and the patient's hepatic reserve. A number of staging systems are available[2,6-8] but there is no worldwide consensus on a single system. For instance, the Child-Pugh (C-P) classification system and the model for end-stage liver disease score can be used to assess the patient's hepatic reserve and liver function. Besides, the performance status (PS) of patients also needs to be taken into consideration. The Barcelona Clinic Liver Cancer staging and prognostic system accounts for variables related to tumor stage, physical performance, liver functional status, cancer-related symptoms and so on. It may provide the link between diseases and treatment strategies. Curative therapy, including various surgeries (*e.g.*, hepatic resection and liver transplantation), locoregional therapies (percutaneous ethanol injection and radiofrequency ablation), have been proven to have better survival benefits in the very early and early stage of HCC (such as stage 0-A). However, the intermediate stage (*i.e.*, stage B) of HCC comprises a highly heterogeneous patient population and therefore poses challenges for therapeutic management. A sub-classification B1-B4 was recently proposed, taking the C-P score, tumor burden (up to seven criteria), PS and portal vein thrombosis into account[9]. Transarterial chemoembolization (TACE) and radioembolization are the primary options for these patients with preserved liver function (C-P classification A) and PS score 0. Unfortunately, if the HCC has developed into the severely advanced stage, only systemic medical treatment is indicated and the prognosis and outcome is very poor for these patients. In this paper, we will discuss systemic treatment for patients with HCC for whom liver-directed therapy is not appropriate.

SYSTEMIC CYTOTOXIC CHEMOTHERAPY

HCC is highly refractory to conventional cytotoxic chemotherapy. In the last decade, no effective conventional systemic cytotoxic therapy has been available and no single regimen has emerged as superior to any other[10]. The substances related to sensitive of chemotherapy include P-glycoprotein[11-13], glutathione-S-transferase[14], heat shock proteins[15], topoisomerase Ⅱα[16] and p53[17]. Besides resistance, the major side effects of systemic chemotherapy are poorly tolerated by patients with severe hepatic dysfunction. One study which enrolled 147 previously untreated HCC patients demonstrated that patients with significant cirrhosis (ascites, serum total bilirubin more than 2.0 mg/dL), performance status of 2-3, a tumor occupying more than 50% of the entire liver and tumor thrombus in the main portal trunk may not be responsive to chemotherapy[18]. The regimens of systemic chemotherapy for HCC under clinical study are as follow: monotherapy regimens, including doxorubicin, mitoxantrone, fluoropyrimidines, gemcitabine, irinotecan and thalidomide; combination chemotherapy, including cisplatin-based, gemcitabine-based and oxaliplatin-based regimens; and PIAF regimen [cisplatin (P)/interferon α-2b (I)/doxorubicin (A)/fluorouracil (F)]. Most published studies of systemic chemotherapy revealed that the effective response rates were no more than 25% and there is no evidence that it may improve the overall survival rate in patients with any subset of HCC[19-21]. However, chemotherapy may still be considered for patients whose tumors progress while on sorafenib treatment. Cytotoxic

therapy should be reserved for medically appropriate patients with adequate hepatic function. The national comprehensive cancer network guidelines (version 2, 2014) recommended that systemic or intra-arterial chemotherapy can be used to treat patients with unresectable HCC by surgery and not a transplant candidate only in the context of a clinical trial[22].

MOLECULARLY TARGETED THERAPY

Hepatocarcinogenesis is a very complex system of pathways and the result of the genetic alterations that may affect multiple signaling cascades. All these pathways include various growth factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor and regulating specific intracellular pathway (RAF/MEK/ERK pathway). For example, the activation of the RAF/MEK/ERK pathway may lead to the growth of HCC. The EGF would bind to its cognate receptor EGF receptor and trigger signal transduction through the RAF/MEK/ERK pathway. Besides, VEGF may result in HCC angiogenesis and HGF will bind to the c-MET receptor and other molecular signal pathways, including PI3K/PTEN/Akt/mammalian target of rapamycin (mTOR) and Wnt/β-catenin pathways. Recently, many medical doctors and scientists have focused on targeted molecular agents (*e.g.*, sorafenib) and tried to block one or more steps in carcinogenic pathways for retardation of tumor formation[23,24].

Until now, sorafenib has been very popular for patients with the advanced stage of HCC. Clinically, sorafenib is an oral form and belongs to the multi-targeted tyrosine kinase inhibitors (multi-kinase inhibitors) and anti-angiogenic agents. It may inhibit abnormal growth of multiple cell surfaces and intra-cellular kinases which would be involved in angiogenesis, cell proliferation and cellular differentiation. The different kinases include various VEGF receptors (VEGFR-1, 2, 3), platelet-derived growth factor receptor (PDGFR-β), c-KIT and RET. Furthermore, sorafenib was also shown to inhibit the RAF/MEK/ERK pathway[25,26].

Sorafenib is also the first medical therapy to show a statistically significant and clinically meaningful overall survival benefit in advanced HCC and is considered to be a standard therapy as it inhibits growth and angiogenesis of HCC. From the SHARP trial (phase Ⅲ) in many countries in 2008, 602 patients with advanced HCC and C-P classification A cirrhosis were randomly assigned to the sorafenib or placebo group. Improvement of median overall survival (OS) was seen in the sorafenib group (10.7 mo *vs* 7.9 mo, HR = 0.69, $P < 0.001$). Treatment was also associated with an increased time to progression (TTP) (5.5 mo *vs* 2.8 mo, HR = 0.58, 95%CI: 0.45-0.74, $P < 0.001$). Overall toxicity did not differ between the treatment and placebo arm (52% *vs* 54%)[27]. In 2009, another phase Ⅲ trial in the Asia-Pacific region (so called ORIENTAL study) reported 226 patients of advanced HCC with C-P classification A cirrhosis who received sorafenib 400 mg twice daily or placebo. Patients with sorafenib therapy had better median OS (6.5 mo *vs* 4.2 mo) and TTP (2.8 mo *vs* 1.4 mo). Only small side effects about grade 3 or 4, including hand-foot syndrome (11%), diarrhea (6%) and fatigue (3%), were found in patients[28]. These exciting results were encouraging and the better efficacy of sorafenib was validated. Thus, sorafenib was approved by the Food and Drug Administration in November 2007 in the United States and has now become the standard care for first line systemic treatment in advanced hepatocellular carcinoma.

Although sorafenib is the first and only targeted therapy approved for advanced HCC, it has also been studied in combination with other systemic chemotherapeutic agents. For example, in a phase Ⅱ trial, patients with advanced HCC were randomly assigned to receive doxorubicin in combination with sorafenib or doxorubicin alone[29]. The combination of doxorubicin and sorafenib improved median TTP (6.4 mo *vs* 2.8 mo, $P = 0.02$), median OS (13.7 mo *vs* 6.5 mo, $P = 0.006$) and progression-free survival (PFS) (6.0 mo *vs* 2.7 mo, $P = 0.006$), compared to doxorubicin alone. However, the effects and mechanisms of doxorubicin in this synergism still remained unclear. Recently, another phase Ⅲ drug trial comparing the combination of doxorubicin and sorafenib with sorafenib alone conducted by the National Cancer Institute is still ongoing. Combination of sorafenib with other systemic agents, such as octreotide[30], has been reported. All of these trials reported improved OS when compared to sorafenib alone; however, the sample sizes were small. The exact and final outcomes deserve intervention.

The worry about the drug resistance of sorafenib has attracted attention. The primary resistance mechanism is possibly due to the genetic heterogeneity and acquired resistance is possibly related to activation of the compensatory pathways, such as the PI3K/Akt and JAK-STAT pathways, tumor hypoxia, EMT, *etc.*[31]. The mechanisms for the resistance of HCC to sorafenib are complicated and remain unclear and need further study.

OTHER ANTIANGIOGENIC AGENTS IN CLINICAL DEVELOPMENT

Sunitinib

A variety of oral multiple tyrosine kinase inhibitors have been recently developed after the impact of sorafenib. Other oral, small molecule, multi-targeted receptor tyrosine kinases, so called, were developed. This agent was proved to inhibit the VEGFR (1, 2, 3), PDGFRs, KIT, RET and the fms-like tyrosine kinase-3 receptor. Some of these factors pay a role in both tumor angiogenesis and tumor cell proliferation. When we used sunitinib to treat patients with advanced HCC, the simultaneous inhibition of these targets therefore led to reduced tumor sizes, vascularization cancer cell death and even tumor shrinkage ultimately.

Indeed, most of the side effects from sunitinib are very mild, including fatigue, diarrhea, nausea and anorexia. In an initial phase Ⅱ trial, 37 patients with advanced HCC were treated with sunitinib. Only one patient had a partial response and 35% of patients were stable[32]. However, grade 3 to 4 toxicity from agents was prominent, including thrombocytopenia (37.8%), neutropenia (24.3%), asthenia (13.5%), hand-foot syndrome (10.8%) and anemia (10.8%) in some patients. Fatal treatment-related adverse events were reported in four patients (10.8%). Therefore, more attention should be paid to this event when treating patients. A phase Ⅲ trial of 1074 patients with advanced HCC disclosed that sunitinib was not superior to sorafenib, with a worse median OS (7.9 mo *vs* 10.2 mo) and more toxicity[33].

Linifanib

Linifanib is a multi-kinase inhibitor targeting VEGFR and PDGFR. In a phase Ⅱ trial involving 44 patients (of which 89% were Asian), the single agent linifanib was found to be clinically active in patients with advanced HCC, with an acceptable safety profile[34]. However, in a phase Ⅲ study, 1000 patients with advanced HCC and C-P classification A cirrhosis were randomly assigned to linifanib or sorafenib treatment. The median OS was 9.1 mo in the linifanib group, compared to 9.8 mo in the sorafenib group. TTP was 5.4 mo *vs* 4.0 mo (P = 0.001) in the linifanib group *vs* the sorafenib group[35]. Although linifanib had a longer TTP, its superiority in survival needs to be verified.

Brivanib

Brivanib is a selective dual receptor inhibitor against fibroblastic growth factor receptor and VEGFR. It was shown to have antitumor activity in patients with advanced HCC in two phase Ⅱ studies[36,37]. In a phase Ⅲ trial, brivanib was reported to have an OS of 9.4 mo *vs* 8.2 mo in the placebo group (as a second line treatment), which was not statistically significant (P = 0.33)[38]. Another phase Ⅲ trial compared brivanib with sorafenib as first line treatment[39]. Among 1150 patients with advanced HCC, the median OS was 9.5 mo in the brivanib group and 9.9 mo in the sorafenib group, with no statistically significant difference. However, brivanib was less well tolerated than sorafenib. Treatment discontinued due to side effects was 43% in the brivanib group compared to 33% of the sorafenib group[39].

OTHER INVESTIGATIONAL APPROACHES IN TARGETED KINASE INHIBITORS

Newer molecularly targeted studies are being developed in phase 1/2 studies, including everolimus, targeting inhibitors of the mTOR[40,41] and inhibitors of HGF/c-Met, such as tivantinib[42]. The single arm, phase 1/2 study of everolimus enrolled 28 patients with advanced HCC and defined 10 mg/d as the phase Ⅱ dosage[40]. The median PFS and OS were 3.8 mo and 8.4 mo, respectively. Another phase Ⅰ study enrolled 39 patients with advanced or metastatic HCC and recommended everolimus dosing of 7.5 mg daily[41]. The phase Ⅱ study reported that TTP was longer in the tivantinib group than in the placebo group (1.6 mo *vs* 1.4 mo)[42]. For patients with MET-high tumors, the TTP was longer in the tivantinib group than in the placebo group (2.7 mo *vs* 1.4 mo). The most common grade 3 adverse events in the tivantinib group were neutropenia (14%) and anemia (11%). The study recommended tivantinib as an option for second-line treatment of patients with advanced HCC. Further phase Ⅲ trials are needed.

ANTIANGIOGENIC AGENTS AS TACE ENHANCERS

TACE consumes blood and causes hypoxia in patients with HCC. However, only the deeply hypoxic area in HCC died and other limited hypoxic areas survived. This is caused by the extra-hepatic collateral arteries supply for HCC if the tumors are large or peripherally located. The development of these vessels interferes with effective control of the tumor with TACE[43]. This result of a high rate of tumor recurrence and low rate of long-term survival is still common in patients with unresectable HCC. Post-TACE recurrences may be due to angiogenesis enhancement and upregulation of VEGF induced by TACE[44,45]. Therefore, new treatment strategies for patients with unresectable HCC are needed, including the optimization of TACE with combination of other modalities. TACE has currently become the standard treatment for patients with intermediate HCC. However, for patients unsuitable for TACE or in whom TACE resulted in unacceptable toxicity, the use of oral sorafenib is another choice[46-49]. Some trials have focused on the combination of TACE and sorafenib. One meta-analysis confirmed that the combination therapy of TACE and sorafenib can improve the OS (HR = 0.65, 95%CI: 0.47-0.89, P = 0.007), TTP (HR = 0.68, 95%CI: 0.52-0.87, P = 0.003) and the objective response rate (HR = 1.06, 95%CI: 1.01-1.12, P = 0.021). Nevertheless, it did not affect the progression of free survival when compared to TACE alone[50]. Besides, the significantly increased risks of adverse reactions from combination therapy were occasionally noted. Another meta-analysis demonstrated that sorafenib combined with TACE may have superiority over TACE alone in terms of TTP. The HR for TTP was found to be 0.76 (P < 0.001) with low heterogeneity in studies (P = 0.243, I^2 = 25.5%)[51]. However, the HR for OS was found to be 0.81 (P = 0.061) with low heterogeneity in studies (P = 0.259, I^2 = 25.4%). Adverse reactions are generally manageable with dose reductions. However, one phase Ⅲ trial enrolled 458 previously TACE-treated patients and the median TTP in the sorafenib and placebo groups was 5.4 and 3.7 mo (HR = 0.87, P = 0.252). HR for OS was 1.06 (P = 0.790). Thus, sorafenib did not

significantly prolong TTP in patients who responded to TACE[52]. The efficacy of TACE plus sorafenib still needs confirmation with further studies.

NEW DIRECTION FOR MOLECULARLY TARGETED THERAPY

Both *in vitro* and *in vivo* studies have shown that sorafenib may promote anti-proliferative and pro-apoptotic effects in tumor cells as well as in endothelial cells. However, it appears that the molecular mechanisms underlying the direct effects of sorafenib in these cells are not completely understood and probably involve additional pathways. Chen *et al*[53] reported that sorafenib sensitizes HCC cells to tumor necrosis factor related apoptosis, inducing ligand (TRAIL) through the inhibition of signal transducer and activator of transcription 3 (STAT3). Tai *et al*[54] demonstrated that sorafenib would inhibit the development of HCC *via* the kinase-independent mechanism, SHP-1 dependent STAT3 inactivation. STAT3 is a transcription factor that modulates survival-directed transcription. In cancer cells, STAT3 can be activated by overactive receptors, including interleukin-6, EGF family members or HGF. In some research, it could be seen that TAT3-stimulated genes may promote angiogenesis, proliferation and survival. In addition, the STAT3 activation could also turn on the strong negative feedback loops involving tyrosine phosphatases (SHP-1 and SHP-2) and suppressors of cytokine signaling. By reducing the levels of STAT3 phosphorylation (Tyr^{705} - STAT3 phosphorylation), the phosphatases would block STAT3 dimerization and transcriptional activity[55,56]. The literature has shown that sorafenib may reduce STAT3 phosphorylation and induce cell death. A series of sorafenib derivatives were synthesized as new inhibitors for STAT3 phosphorylation. Such results provide a new direction for the designs of anti-HCC drugs[57,58]. Novel sorafenib derivatives (SC-40, SC-43 and SC-60) have been studied *in vitro* and *in vivo*. These sorafenib derivatives induced apoptotic cell death significantly by enhanced SHP-1 activity and inhibited the phosphorylation of STAT3 at the concentration of 0.5 μmol/L, which was more potent than sorafenib (5 μmol/L)[59,60]. These new compounds of sorafenib derivatives appeared to be an important different pathway to sorafenib, more potent and with not only a tumoristatic effect but also a tumorcidal effect.

OTHER AGENTS UNDER STUDY FOR ADVANCED HCC

Hormone therapies

Tamoxifen and megestrol: Many animal models of experimental liver carcinogenesis and epidemiological studies in humans have all suggested the relationship between the sexual hormones and HCC[61]. The intimate connection may be due to estrogen receptors (ERs) present in one-third of HCCs. These tumors could potentially gain benefit from ER blockade with tamoxifen. However, some large randomized trials, including CLIP-1 studies, showed no improvement in survival or functional status advantage when comparing the addition of tamoxifen to best supportive care[62,63]. The possible reasons include the presence of variant ERs in some of these tumors, lack of patient selection, the problem of dosage selection and the fact that tamoxifen in HCC could indeed act *via* an ER-independent pathway[64-66]. The efficacy of megestrol acetate has been evaluated in HCC with variant ER. Better therapeutic benefits were shown in some studies[64,67]. However, in one randomized double blind trial of megestrol acetate *vs* placebo in 204 patients with treatment-naive advanced HCC, megestrol acetate had no role in prolonging OS in advanced treatment-naive HCC[68].

Octreotide: Octreotide is an analogue of the hormone somatostatin. Over 40% of HCC patients may express specific somatostatin receptors (SSTR) and *in vitro* data showed the direct anti-tumor effect of octreotide in HCC[69,70]. The molecular mechanisms involved in the anti-neoplastic activity of somatostatin are related to the direct and indirect growth inhibition mediated by SSTR expressed in the target tissue[71]. In a phase Ⅲ study, octreotide had a favorable safety profile but did not improve OS and could have a negative impact on the quality of life for patients with advanced HCC[72]. A meta-analysis showed that the 6 and 12 mo survival rates in the octreotide group were significantly higher than those of the control group, but only in Eastern studies. They concluded that octreotide could improve the survival rates of patients with advanced HCC, but possibly not in Western countries[73]. The results are still controversial so routine administration of octreotide cannot be recommended.

Immunotherapy anti-programmed death-1

Human endogenous immunity responses can recognize many cancer cells as non-self and these kinds of responses have been observed in preclinical models and patients. However, these responses are ineffective because of the tumor's own multiple resistance mechanisms, including systemic dysfunction in T-cell signaling[74]. For instance, programmed death 1 (PD-1), the T-cell co-inhibitory receptor with its known ligand PD-L1 (known as B7-H1), plays an important role in mediating immunosuppression and has been involved in multiple immunopathological scenarios[75]. Many studies have shown that the PD-1/PD-L1 pathway was also the important factor in compromised tumor immunity. If the blockade of this pathway by anti-PD-L1 antibodies occurred, we could easily enhance the antitumor abilities and inhibit tumor growth in several cancers, such as melanoma, non-small cell lung cancer and renal cell carcinoma[76]. Thus, PD-L1 was demonstrated to deliver an inhibitory signal to PD-1 expressing T cells leading to the suppression of the immune response by inducing apoptosis, unresponsiveness and functional exhaustion

of T cells[77,78]. The dose escalation study of anti-PD-1 monoclonal antibody BMS-936558 was administered as a single dose in 39 patients with advanced solid tumors. A favorable safety profile and preliminary evidence of clinical activity were shown in this pilot study, establishing the basis for the current multiple dose trial involving patients with diverse cancers[79]. In chronic HBV patients, peripheral HBV-specific $CD8^+$ T-cells are mostly PD-1 positive and functionally impaired, with restoration of their effector function after blocking the PD-1/PD-L1 pathway. The analogous condition was also seen in chronic HCV patients[80,81]. The levels of PD-1(+)/CD8(+) T cells may apparently increase with disease progression from patients with liver cirrhosis to HCC *vs* the healthy control[82]. B7-H1, PD-1(+), CD8(+) T cells axis contributes to immune suppression in human HCC, with blockade of this pathway carrying therapeutic implications. Various studies have demonstrated the relationships between the expression of intrahepatic PD-1 on T-cells and postoperative recurrence, the stage of tumor and the prognosis of diseases[80,82]. Thus, monoclonal antibodies against both PD-L1 and PD-1 have been developed.

Oncolytic virotherapy

Replication-selective tumor-specific viruses present a new treatment direction for neoplastic disease which is facilitated by virus-mediated lysis of tumor cells after selective viral propagation within the tumor. The selectivity for cancer cells is derived from a human telomerase reverse transcriptase (hTERT) promoter-driven active viral replication, which only occurs in cancer cells with high telomerase activity. For example, telomelysin is a telomerase-specific replication-competent oncolytic adenovirus that may replicate efficiently and induce marked cell killing in human cancer cells[83]. However, the TERT activity is elevated in most cases of HCC and thus all current studies aim to investigate whether telomelysin can be used for the treatment of HCC or not[84]. Telomerase-specific oncolytic virotherapy has been studied *in vivo* to show that it is cancer-selective, replication-competent and causes the oncolysis of liver cancer cells[85]. In a preclinical *in vivo* study of the orthotopic HCC model, the telomelysin agent showed the potent oncolytic effect on HCC but spared normal liver tissue. The effects of multiple injections of telomelysin were also evaluated recently. Lin *et al*[86] concluded that telomelysin can be used for treatment of human HCC at an appropriate dosage and that its tumor-killing activity persists after multiple injections.

CONCLUSION

Treatment of human HCC is a multidisciplinary, patient-oriented strategy and must take the patient's clinical stage, liver function reserve and performance status into consideration in detail. Multiple chemotherapeutic agents have been used both as single agents and in combination to treat advanced HCC but, until recently, none of them had been shown to improve overall survival effectively. Now, the multi-kinase inhibitor "sorafenib" is still the only approved drug for patients with advanced HCC. However, there are also many mechanisms involving molecular signaling pathways which may identify different targets for novel molecular therapies that remain unknown. Thus, the efficacy of combination of anti-angiogenic agents plus TACE still needs more confirmation. Besides, immunotherapy with anti-PD-1 and oncolytic virotherapy also have therapeutic potential but need approval by further clinical studies and clues. To our knowledge, the importance of effective systemic therapies for patients with advanced HCC is clear now and more effort is required to advance talent in the future.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998; **28**: 751-755 [PMID: 9731568 DOI: 10.1002/hep.510280322]

3 **Venook AP**, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist* 2010; **15** Suppl 4: 5-13 [PMID: 21115576 DOI: 10.1634/theoncologist.2010-S4-05]

4 **Beasley RP**. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988; **61**: 1942-1956 [PMID: 2834034 DOI: 10.1002/1097-0142(19880515)61:10<1942::AID-CNCR-2820611003>3.0.CO;2-J]

5 **Altekruse SF**, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; **27**: 1485-1491 [PMID: 19224838 DOI: 10.1200/jco.2008.20.7753]

6 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]

7 **Leung TW**, Tang AM, Zee B, Lau WY, Lai PB, Leung KL, Lau JT, Yu SC, Johnson PJ. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. *Cancer* 2002; **94**: 1760-1769 [PMID: 11920539 DOI: 10.1002/cncr.10384]

8 **Kudo M**, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). *J Gastroenterol* 2003; **38**: 207-215 [PMID: 12673442 DOI: 10.1007/s005350300038]

9 **Bolondi L**, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012; **32**: 348-359 [PMID: 23397536 DOI: 10.1055/s-0032-1329906]

10 **Lopez PM**, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma--an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2006; **23**: 1535-1547 [PMID: 16696801 DOI: 10.1111/j.1365-2036.2006.02932.x]

11 **Huang C**, Xu D, Xia Q, Wang P, Rong C, Su Y. Reversal of P-glycoprotein-mediated multidrug resistance of human hepatic cancer cells by Astragaloside II. *J Pharm Pharmacol* 2012; **64**: 1741-1750 [PMID: 23146037 DOI: 10.1111/j.2042-7158.2012.01549.x]

12 **Soini Y**, Virkajärvi N, Raunio H, Pääkkö P. Expression of P-glycoprotein in hepatocellular carcinoma: a potential marker of prognosis. *J Clin Pathol* 1996; **49**: 470-473 [PMID: 8763260 DOI: 10.1136/jcp.49.6.470]

13 **Fardel O**, Loyer P, Lecureur V, Glaise D, Guillouzo A. Constitutive expression of functional P-glycoprotein in rat hepatoma cells. *Eur J Biochem* 1994; **219**: 521-528 [PMID: 7905826]

14 **Li CG**, Zhao ZM, Hu MG, Liu R. Predictive role of glutathione-S-transferase gene polymorphisms in risk and prognosis of hepatocellular carcinoma. *Asian Pac J Cancer Prev* 2012; **13**: 3247-3252 [PMID: 22994742 DOI: 10.7314/APJCP.2012.13.7.3247]

15 **Lv LH**, Wan YL, Lin Y, Zhang W, Yang M, Li GL, Lin HM, Shang CZ, Chen YJ, Min J. Anticancer drugs cause release of exosomes with heat shock proteins from human hepatocellular carcinoma cells that elicit effective natural killer cell antitumor responses in vitro. *J Biol Chem* 2012; **287**: 15874-15885 [PMID: 22396543 DOI: 10.1074/jbc.M112.340588]

16 **Chen MC**, Chen CH, Chuang HC, Kulp SK, Teng CM, Chen CS. Novel mechanism by which histone deacetylase inhibitors facilitate topoisomerase IIα degradation in hepatocellular carcinoma cells. *Hepatology* 2011; **53**: 148-159 [PMID: 21254166 DOI: 10.1002/hep.23964]

17 **Chan KT**, Lung ML. Mutant p53 expression enhances drug resistance in a hepatocellular carcinoma cell line. *Cancer Chemother Pharmacol* 2004; **53**: 519-526 [PMID: 15004724 DOI: 10.1007/s00280-004-0767-4]

18 **Nagahama H**, Okada S, Okusaka T, Ishii H, Ikeda M, Nakasuka H, Yoshimori M. Predictive factors for tumor response to systemic chemotherapy in patients with hepatocellular carcinoma. *Jpn J Clin Oncol* 1997; **27**: 321-324 [PMID: 9390209 DOI: 10.1093/jjco/27.5.321]

19 **Nowak AK**, Chow PK, Findlay M. Systemic therapy for advanced hepatocellular carcinoma: a review. *Eur J Cancer* 2004; **40**: 1474-1484 [PMID: 15196530 DOI: 10.1016/j.ejca.2004.02.027]

20 **Palmer DH**, Hussain SA, Johnson PJ. Systemic therapies for hepatocellular carcinoma. *Expert Opin Investig Drugs* 2004; **13**: 1555-1568 [PMID: 15566313 DOI: 10.1517/13543784.13.12.1555]

21 **Thomas MB**, O'Beirne JP, Furuse J, Chan AT, Abou-Alfa G, Johnson P. Systemic therapy for hepatocellular carcinoma: cytotoxic chemotherapy, targeted therapy and immunotherapy. *Ann Surg Oncol* 2008; **15**: 1008-1014 [PMID: 18236117 DOI: 10.1245/s10434-007-9705-0]

22 **National Comprehensive Cancer Network**. National Comprehensive Cancer Network guidelines for hepatobiliary cancer. Version 2. [Accessed 2014]. Available from: URL: http://www.nccn.org/

23 **Raza A**, Sood GK. Hepatocellular carcinoma review: current treatment, and evidence-based medicine. *World J Gastroenterol* 2014; **20**: 4115-4127 [PMID: 24764650 DOI: 10.3748/wjg.v20.i15.4115]

24 **Kudo M**. Signaling pathway/molecular targets and new targeted agents under development in hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 6005-6017 [PMID: 23155330 DOI: 10.3748/wjg.v18.i42.6005]

25 **Wilhelm S**, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R, Kelley S. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov* 2006; **5**: 835-844 [PMID: 17016424]

26 **Liu L**, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, Wilhelm S, Lynch M, Carter C. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006; **66**: 11851-11858 [PMID: 17178882 DOI: 10.1158/0008-5472.can-06-1377]

27 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

28 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

29 **Abou-Alfa GK**, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, Gansukh B, Saltz LB. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA* 2010; **304**: 2154-2160 [PMID: 21081728 DOI: 10.1001/jama.2010.1672]

30 **Prete SD**, Montella L, Caraglia M, Maiorino L, Cennamo G, Montesarchio V, Piai G, Febbraro A, Tarantino L, Capasso E, Palmieri G, Guarrasi R, Bianco M, Mamone R, Savastano C, Pisano A, Vincenzi B, Sabia A, D'Agostino A, Faiola V, Addeo R. Sorafenib plus octreotide is an effective and safe treatment in advanced hepatocellular carcinoma: multicenter phase II So.LAR. study. *Cancer Chemother Pharmacol* 2010; **66**: 837-844 [PMID: 20041325 DOI: 10.1007/s00280-009-1226-z]

31 **Zhai B**, Sun XY. Mechanisms of resistance to sorafenib and the corresponding strategies in hepatocellular carcinoma. *World J Hepatol* 2013; **5**: 345-352 [PMID: 23898367 DOI: 10.4254/wjh.v5.i7.345]

32 **Faivre S**, Raymond E, Boucher E, Douillard J, Lim HY, Kim JS, Zappa M, Lanzalone S, Lin X, Deprimo S, Harmon C, Ruiz-Garcia A, Lechuga MJ, Cheng AL. Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study. *Lancet Oncol* 2009; **10**: 794-800 [PMID: 19586800 DOI: 10.1016/S1470-2045(09)70171-8]

33 **Cheng AL**, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Lanzalone S, Yang L, Lechuga MJ, Raymond E. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; **31**: 4067-4075 [PMID: 24081937 DOI: 10.1200/JCO.2012.45.8372]

34 **Toh HC**, Chen PJ, Carr BI, Knox JJ, Gill S, Ansell P, McKeegan EM, Dowell B, Pedersen M, Qin Q, Qian J, Scappaticci FA, Ricker JL, Carlson DM, Yong WP. Phase 2 trial of linifanib (ABT-869) in patients with unresectable or metastatic hepatocellular carcinoma. *Cancer* 2013; **119**: 380-387 [PMID: 22833179 DOI: 10.1002/cncr.27758]

35 **Cainap C**, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Eskens F, Qian J, McKee MD, Ricker JL, Carlson DM, Nowiem SE. Phase III trial of linifanib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2013; **31** Suppl 4: abstr 249

36 **Finn RS**, Kang YK, Mulcahy M, Polite BN, Lim HY, Walters I, Baudelet C, Manekas D, Park JW. Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012; **18**: 2090-2098 [PMID: 22238246 DOI: 10.1158/1078-0432.ccr-11-1991]

37 **Park JW**, Finn RS, Kim JS, Karwal M, Li RK, Ismail F, Thomas M, Harris R, Baudelet C, Walters I, Raoul JL. Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2011; **17**: 1973-1983 [PMID: 21349999 DOI: 10.1158/1078-0432.ccr-10-2011]

38 **Llovet JM**, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013; **31**: 3509-3516 [PMID: 23980090 DOI: 10.1200/JCO.2012.47.3009]

39 **Johnson PJ**, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Aviña J, Kudo M, Yan L, Sobhonslidsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine R, Walters

I, Cheng AL. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; **31**: 3517-3524 [PMID: 23980084 DOI: 10.1200/JCO.2012.48.4410]

40 **Zhu AX**, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, Zheng H, Muzikansky A, Clark JW, Kwak EL, Schrag D, Jors KR, Fuchs CS, Iafrate AJ, Borger DR, Ryan DP. Phase 1/2 study of everolimus in advanced hepatocellular carcinoma. *Cancer* 2011; **117**: 5094-5102 [PMID: 21538343 DOI: 10.1002/cncr.26165]

41 **Shiah HS**, Chen CY, Dai CY, Hsiao CF, Lin YJ, Su WC, Chang JY, Whang-Peng J, Lin PW, Huang JD, Chen LT. Randomised clinical trial: comparison of two everolimus dosing schedules in patients with advanced hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013; **37**: 62-73 [PMID: 23134470 DOI: 10.1111/apt.12132]

42 **Santoro A**, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa G, Schwartz B, Von Roemeling R, Lamar ME, Chen Y, Porta C. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol* 2013; **14**: 55-63 [PMID: 23182627 DOI: 10.1016/S1470-2045(12)70490-4]

43 **Kim HC**, Chung JW, Lee W, Jae HJ, Park JH. Recognizing extrahepatic collateral vessels that supply hepatocellular carcinoma to avoid complications of transcatheter arterial chemoembolization. *Radiographics* 2005; **25** Suppl 1: S25-S39 [PMID: 16227494 DOI: 10.1148/rg.25si055508]

44 **Li X**, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. *World J Gastroenterol* 2004; **10**: 2878-2882 [PMID: 15334691]

45 **Wang B**, Xu H, Gao ZQ, Ning HF, Sun YQ, Cao GW. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. *Acta Radiol* 2008; **49**: 523-529 [PMID: 18568538 DOI: 10.1080/02841850801958890]

46 **Raoul JL**, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, Lencioni R. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev* 2011; **37**: 212-220 [PMID: 20724077 DOI: 10.1016/j.ctrv.2010.07.006]

47 **Park JW**, Koh YH, Kim HB, Kim HY, An S, Choi JI, Woo SM, Nam BH. Phase II study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. *J Hepatol* 2012; **56**: 1336-1342 [PMID: 22314421 DOI: 10.1016/j.jhep.2012.01.006]

48 **Dufour JF**. TACE with or without systemic therapy? *J Hepatol* 2012; **56**: 1224-1225 [PMID: 22402292 DOI: 10.1016/j.jhep.2012.02.011]

49 **Farinati F**, Giacomin A, Vanin V, Giannini E, Trevisani F. TACE treatment in hepatocellular carcinoma: what should we do now? *J Hepatol* 2012; **57**: 221-222 [PMID: 22286000 DOI: 10.1016/j.jhep.2011.12.022]

50 **Zhang L**, Hu P, Chen X, Bie P. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepatocellular carcinoma: a meta-analysis. *PLoS One* 2014; **9**: e100305 [PMID: 24945380 DOI: 10.1371/journal.pone.0100305]

51 **Liu L**, Chen H, Wang M, Zhao Y, Cai G, Qi X, Han G. Combination therapy of sorafenib and TACE for unresectable HCC: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e91124 [PMID: 24651044 DOI: 10.1371/journal.pone.0091124]

52 **Kudo M**, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, Yoon JH, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh DJ, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; **47**: 2117-2127 [PMID: 21664811 DOI: 10.1016/j.ejca.2011.05.007]

53 **Chen KF**, Tai WT, Liu TH, Huang HP, Lin YC, Shiau CW, Li PK, Chen PJ, Cheng AL. Sorafenib overcomes TRAIL resistance of hepatocellular carcinoma cells through the inhibition of STAT3. *Clin Cancer Res* 2010; **16**: 5189-5199 [PMID: 20884624 DOI: 10.1158/1078-0432.ccr-09-3389]

54 **Tai WT**, Cheng AL, Shiau CW, Huang HP, Huang JW, Chen PJ, Chen KF. Signal transducer and activator of transcription 3 is a major kinase-independent target of sorafenib in hepatocellular carcinoma. *J Hepatol* 2011; **55**: 1041-1048 [PMID: 21354226 DOI: 10.1016/j.jhep.2011.01.047]

55 **Rosmorduc O**, Desbois-Mouthon C. Targeting STAT3 in hepatocellular carcinoma: sorafenib again. *J Hepatol* 2011; **55**: 957-959 [PMID: 21718664 DOI: 10.1016/j.jhep.2011.06.005]

56 **Yang SF**, Wang SN, Wu CF, Yeh YT, Chai CY, Chunag SC, Sheen MC, Lee KT. Altered p-STAT3 (tyr705) expression is associated with histological grading and intratumour microvessel density in hepatocellular carcinoma. *J Clin Pathol* 2007; **60**: 642-648 [PMID: 16901975 DOI: 10.1136/jcp.2006.036970]

57 **Chen KF**, Tai WT, Huang JW, Hsu CY, Chen WL, Cheng AL, Chen PJ, Shiau CW. Sorafenib derivatives induce apoptosis through inhibition of STAT3 independent of Raf. *Eur J Med Chem* 2011; **46**: 2845-2851 [PMID: 21531053 DOI: 10.1016/j.ejmech.2011.04.007]

58 **Chen KF**, Tai WT, Hsu CY, Huang JW, Liu CY, Chen PJ, Kim I, Shiau CW. Blockade of STAT3 activation by sorafenib derivatives through enhancing SHP-1 phosphatase activity. *Eur J Med Chem* 2012; **55**: 220-227 [PMID: 22871485 DOI: 10.1016/j.ejmech.2012.07.023]

59 **Tai WT**, Shiau CW, Chen PJ, Chu PY, Huang HP, Liu CY, Huang JW, Chen KF. Discovery of novel Src homology region 2 domain-containing phosphatase 1 agonists from sorafenib for the treatment of hepatocellular carcinoma. *Hepatology* 2014; **59**: 190-201 [PMID: 23908138 DOI: 10.1002/hep.26640]

60 **Chen KF**, Chen HL, Shiau CW, Liu CY, Chu PY, Tai WT, Ichikawa K, Chen PJ, Cheng AL. Sorafenib and its derivative SC-49 sensitize hepatocellular carcinoma cells to CS-1008, a humanized anti-TNFRSF10B (DR5) antibody. *Br J Pharmacol* 2013; **168**: 658-672 [PMID: 22978563 DOI: 10.1111/j.1476-5381.2012.02212.x]

61 **De Maria N**, Manno M, Villa E. Sex hormones and liver cancer. *Mol Cell Endocrinol* 2002; **193**: 59-63 [PMID: 12161002 DOI: 10.1016/S0303-7207(02)00096-5]

62 Tamoxifen in treatment of hepatocellular carcinoma: a randomised controlled trial. CLIP Group (Cancer of the Liver Italian Programme) *Lancet* 1998; **352**: 17-20 [PMID: 9800740 DOI: 10.1016/S0140-6736(98)01259-8]

63 **Perrone F**, Gallo C, Daniele B, Gaeta GB, Izzo F, Capuano G, Adinolfi LE, Mazzanti R, Farinati F, Elba S, Piai G, Calandra M, Stanzione M, Mattera D, Aiello A, De Sio I, Castiglione F, Russo M, Persico M, Felder M, Manghisi OG, De Maio E, Di Maio M, Pignata S. Tamoxifen in the treatment of hepatocellular carcinoma: 5-year results of the CLIP-1 multicentre randomised controlled trial. *Curr Pharm Des* 2002; **8**: 1013-1019 [PMID: 11945148 DOI: 10.2174/1381612024607063]

64 **Villa E**, Ferretti I, Grottola A, Buttafoco P, Buono MG, Giannini F, Manno M, Bertani H, Dugani A, Manenti F. Hormonal therapy with megestrol in inoperable hepatocellular carcinoma characterized by variant oestrogen receptors. *Br J Cancer* 2001; **84**: 881-885 [PMID: 11286465 DOI: 10.1054/bjoc.2000.1534]

65 **Villa E**, Dugani A, Fantoni E, Camellini L, Buttafoco P, Grottola A, Pompei G, De Santis M, Ferrari A, Manenti F. Type of estrogen receptor determines response to antiestrogen therapy. *Cancer Res* 1996; **56**: 3883-3885 [PMID: 8752151]

66 **Di Maio M**, De Maio E, Morabito A, D'Aniello R, De Feo G, Gallo C, Perrone F. Hormonal treatment of human hepatocellular carcinoma. *Ann N Y Acad Sci* 2006; **1089**: 252-261 [PMID: 17261772 DOI: 10.1196/annals.1386.007]

67 **Farinati F**, Gianni S, De Giorgio M, Fiorentini S. Megestrol treatment

in patients with hepatocellular carcinoma. *Br J Cancer* 2001; **85**: 1606-1608 [PMID: 11720452 DOI: 10.1054/bjoc.2001.2092]

68 **Chow PK**, Machin D, Chen Y, Zhang X, Win KM, Hoang HH, Nguyen BD, Jin MY, Lobo R, Findlay M, Lim CH, Tan SB, Gandhi M, Soo KC. Randomised double-blind trial of megestrol acetate vs placebo in treatment-naive advanced hepatocellular carcinoma. *Br J Cancer* 2011; **105**: 945-952 [PMID: 21863030 DOI: 10.1038/bjc.2011.333]

69 **Liu HL**, Huo L, Wang L. Octreotide inhibits proliferation and induces apoptosis of hepatocellular carcinoma cells. *Acta Pharmacol Sin* 2004; **25**: 1380-1386 [PMID: 15456543]

70 **Xidakis C**, Kolios G, Valatas V, Notas G, Mouzas I, Kouroumalis E. Effect of octreotide on apoptosis-related proteins in rat Kupffer cells: a possible anti-tumour mechanism. *Anticancer Res* 2004; **24**: 833-841 [PMID: 15161035]

71 **Samonakis DN**, Notas G, Christodoulakis N, Kouroumalis EA. Mechanisms of action and resistance of somatostatin analogues for the treatment of hepatocellular carcinoma: a message not well taken. *Dig Dis Sci* 2008; **53**: 2359-2365 [PMID: 18273705 DOI: 10.1007/s10620-007-0175-9]

72 **Barbare JC**, Bouché O, Bonnetain F, Dahan L, Lombard-Bohas C, Faroux R, Raoul JL, Cattan S, Lemoine A, Blanc JF, Bronowicki JP, Zarski JP, Cazorla S, Gargot D, Thevenot T, Diaz E, Bastie A, Aparicio T, Bedenne L. Treatment of advanced hepatocellular carcinoma with long-acting octreotide: a phase III multicentre, randomised, double blind placebo-controlled study. *Eur J Cancer* 2009; **45**: 1788-1797 [PMID: 19303768 DOI: 10.1016/j.ejca.2009.02.018]

73 **Ji XQ**, Ruan XJ, Chen H, Chen G, Li SY, Yu B. Somatostatin analogues in advanced hepatocellular carcinoma: an updated systematic review and meta-analysis of randomized controlled trials. *Med Sci Monit* 2011; **17**: RA169-RA176 [PMID: 21804474 DOI: 10.12659/MSM.881892]

74 **Topalian SL**, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. *J Clin Oncol* 2011; **29**: 4828-4836 [PMID: 22042955 DOI: 10.1200/JCO.2011.38.0899]

75 **Wu K**, Kryczek I, Chen L, Zou W, Welling TH. Kupffer cell suppression of CD8+ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. *Cancer Res* 2009; **69**: 8067-8075 [PMID: 19826049 DOI: 10.1158/0008-5472.can-09-0901]

76 **Topalian SL**, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**: 2443-2454 [PMID: 22658127 DOI: 10.1056/NEJMoa1200690]

77 **Dong H**, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002; **8**: 793-800 [PMID: 12091876 DOI: 10.1038/nm730]

78 **Freeman GJ**, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, Horton HF, Fouser L, Carter L, Ling V, Bowman MR, Carreno BM, Collins M, Wood CR, Honjo T. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000; **192**: 1027-1034 [PMID: 11015443 DOI: 10.1084/jem.192.7.1027]

79 **Bristol-Myers Squibb**. Dose escalation study of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in patients (Pts) with advanced hepatocellular carcinoma (HCC) with or without chronic viral hepatitis (Anti-PD-1 HCC). [Updated 2015 Feb 16]. Available from: URL: http://clinicaltrials.gov/ct2/show/results/NCT01658878

80 **Boni C**, Fisicaro P, Valdatta C, Amadei B, Di Vincenzo P, Giuberti T, Laccabue D, Zerbini A, Cavalli A, Missale G, Bertoletti A, Ferrari C. Characterization of hepatitis B virus (HBV)-specific T-cell dysfunction in chronic HBV infection. *J Virol* 2007; **81**: 4215-4225 [PMID: 17287266 DOI: 10.1128/JVI.02844-06]

81 **Penna A**, Pilli M, Zerbini A, Orlandini A, Mezzadri S, Sacchelli L, Missale G, Ferrari C. Dysfunction and functional restoration of HCV-specific CD8 responses in chronic hepatitis C virus infection. *Hepatology* 2007; **45**: 588-601 [PMID: 17326153 DOI: 10.1002/hep.21541]

82 **Shi F**, Shi M, Zeng Z, Qi RZ, Liu ZW, Zhang JY, Yang YP, Tien P, Wang FS. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. *Int J Cancer* 2011; **128**: 887-896 [PMID: 20473887 DOI: 10.1002/ijc.25397]

83 **Fujiwara T**, Urata Y, Tanaka N. Telomerase-specific oncolytic virotherapy for human cancer with the hTERT promoter. *Curr Cancer Drug Targets* 2007; **7**: 191-201 [PMID: 17346111 DOI: 10.2174/156800907780058835]

84 **Kawakami Y**, Kitamoto M, Nakanishi T, Yasui W, Tahara E, Nakayama J, Ishikawa F, Tahara H, Ide T, Kajiyama G. Immunohistochemical detection of human telomerase reverse transcriptase in human liver tissues. *Oncogene* 2000; **19**: 3888-3893 [PMID: 10951582 DOI: 10.1038/sj.onc.1203733]

85 **Li YM**, Song ST, Jiang ZF, Zhang Q, Su CQ, Liao GQ, Qu YM, Xie GQ, Li MY, Ge FJ, Qian QJ. Telomerase-specific oncolytic virotherapy for human hepatocellular carcinoma. *World J Gastroenterol* 2008; **14**: 1274-1279 [PMID: 18300357 DOI: 10.3748/wjg.14.1274]

86 **Lin WH**, Yeh SH, Yang WJ, Yeh KH, Fujiwara T, Nii A, Chang SS, Chen PJ. Telomerase-specific oncolytic adenoviral therapy for orthotopic hepatocellular carcinoma in HBx transgenic mice. *Int J Cancer* 2013; **132**: 1451-1462 [PMID: 22886913 DOI: 10.1002/ijc.27770]

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