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Review

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Treatment options after sorafenib failure in patients with hepatocellular carcinoma

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Second line therapy after failure of sorafenib continues to be under study. Prognosis of hepatocellular carcinoma is measured in months, with median overall survival reaching 10.7 months with sorafenib. Because of the modest net benefit sorafenib has contributed, and rising incidence of hepatocellular carcinoma in the world, continued efforts are ongoing to look for efficient upfront, second line, or combination therapies. Herein we review the most relevant to date published literature on treatment options beyond sorafenib, reported studies, ongoing investigational efforts, and possibilities for future studies in advanced hepatocellular carcinoma. **(Clin Mol Hepatol 2017;23:273-279)**

Keywords: Hepatocellular carcinoma; Antiangiogenic therapy; MET-inhibitors; Immunotherapy

INTRODUCTION

Sorafenib remains the only effective first line systemic treatment, with no other approved therapies in the first line yet. Lenvatinib, another antiangiogenic agent, was just shown to be non-inferior to sorafenib. After almost a decade of disappointing results of studies in both first and second line setting, recent data showed improved outcome with regorafenib after progression on sorafenib. The success outcome of regorafenib as an agent by itself or to its sequential use after sorafenib, warrants acknowledgment and a lot of exploration at the biological and molecular level. In the meantime, immunotherapy and c-MET inhibition are continued to be investigated; with the expected results from the immunotherapy standpoint, positioning of these drugs is the next challenge for oncologists. Herein we will discuss the recent results and anticipated ones from a second line perspective.

TARGETING ANGIOGENESIS

Angiogenesis is initiated by destabilization of existing microvasculature, which leads to vascular hyper-permeability, remodeling of the extracellular matrix, and endothelial cell activation. Activated endothelial cells proliferate, migrate, and form new vessels.[1] In hepatocellular carcinoma (HCC), a net excess of angiogenic factors produced by tumor cells, vascular endothelial cells, and immune cells leads to the activation and recruitment of endothelial cells and pericytes[2] The plasma concentration of vascular endothelial growth factor (VEGF), angio-

Abbreviations:

ADI-PEG 20, PEGylated arginine deiminase; AFP, α-fetoprotein; ANGPT, angiopoietin; CI, confidence interval; CTLA, cytotoxic T-lymphocyte-associated protein; EGF, epidermal growth factor; FGF, fibroblast growth factor; FU, Fluorouracil; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HGF, hepatocyte growth factor; IGF, Insulin growth factor; OS, Overall survival; ORR, Objective response rate; PDGF, platelet-derived growth factor; PDL, Programmed Death Ligand; PFS, Progression free survival; TGF, transforming growth factor; TIE-2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2; TKI, Tyrosine kinase inhibitor; TTP, Time to progression; VEGF, vascular endothelial growth factor

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poietin-2 (Ang2), and platelet-derived growth factor (PDGF)-B was found to be increased in patients with HCC compared to cirrhotic patients.[3]

In addition to VEGF, the angiopoietin (ANGPT) family of ligands, ANGPT1 and ANGPT2, bind to the endothelial cell membrane receptor tyrosine kinase TIE2 and contribute to tumor angiogenesis. Concurrent or sequential targeting of the VEGF and angiopoietin pathways is of interest because the strategy could improve efficacy without increasing toxicity.[4] The most common proposed mechanism of resistance is related to the increased level of tumor hypoxia caused by antiangiogenic therapy.[5] For example, inhibition of the VEGF pathway leads to resumption of tumor angiogenesis through upregulation of fibroblast growth factor (FGF)2, interleukin 8, and ANGPT2. Hence, targeting alternative angiogenic pathways is a potential strategy to deal with this mechanism. Another aspect of resistance to antiangiogenic drugs is the potentially reversible (epigenetic) nature of resistance.[6] This change in tyrosine kinase inhibitor (TKI) profile has implications for second-line use of alternate antiangiogenic drugs—e.g., when switching VEGFR TKI in renal cell carcinoma, and more recently in HCC.

Other angiogenic factors potentially involved in liver cancer are placental growth factor (PlGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-α, TGF-β, hepatocyte growth factor (HGF), epidermal growth factor (EGF), IL-4, IL-6, and IL-8.[7]

In view of the successful outcome of sorafenib, an oral multi kinase inhibitor that inhibits VEGFR1-3, PDGFR-α, PDGFR-β, c-KIT, Raf-1 and BRAF, angiogenesis became of the most appealing targets to explore in HCC. Many antiangiogenic agents were explored after progression on sorafenib.

In the phase III multicenter, double-blind, placebo-controlled trial (SHARP) 602 patients with advanced HCC and no previous systemic treatment were randomly assigned to receive either sorafenib (at a dose of 400 mg twice daily) or placebo. Sorafenib showed an improvement in median survival to 10.7 months compared to 7.9 months in the placebo group, (HR=0.69; P<0.001).[8] Of note, sorafenib was reported to be well tolerated among the Korean patients, and survival was in line with the results from the SHARP study.[9] While benefit from sorafenib is observed across patients regardless of disease stage and etiology, subgroup analyses of the phase II[10] and III studies of sorafenib in HCC have implied an improved benefit of sorafenib in patients with hepatitis C virus (HCV)–induced HCC versus other causes.[11] A randomized phase III trial from the Asia-Pacific region[12] involving patients with disease induced mainly by hepatitis B showed that, compared with placebo, sorafenib had a statistically significant survival advantage, but not to the same magnitude as in the SHARP trial (6.5 vs. 4.2 months; P=.014). More recently, a metaanalysis of the phase III randomized trials that demonstrated correlation between sorafenib effect and hepatitis status was reported. It showed improved overall survival (OS) for sorafenib in patients who are both HBV negative and HCV positive (HR, 20.27; 95% CI, 20.46 to 20.06). Median unadjusted survival is 12.6 months for sorafenib and 10.2 months for "other" treatments in this subgroup.[13] The preferential activity of sorafenib in HCV induced HCC, if real, might be due to high RAF kinase activity driven by HCV core protein-1, in this subgroup.[14]

Regorafenib a TKI that targets tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (TIE-2), FGFR, c-kit, and Ret in addition to VEGF, PDGFR, and RAF-MEK-ERK, was evaluated after progression on sorafenib in a randomized, international, multicenter, phase III trial (RESORCE).[15] Study included 573 patients with documented radiological progression during sorafenib treatment who were randomly (2:1) assigned to regorafenib or placebo. Patients were BCLC stage B or C, Child-Pugh A liver function, they must have tolerated prior sorafenib (defined by ≥400 mg daily for at least 20 of the 28 days before discontinuation), and have received their last sorafenib dose within 10 weeks of randomization (median 0.9 month). Median duration of sorafenib therapy was 7.8 months. Study showed clinically and statistically significant improvement in OS (10.6 vs 7.8 months; P<0.001) and progression free survival (PFS) (3.1 vs 1.5 months; P<0.001). Objective responses were achieved by RECIST 1.1, survival benefit was observed across subgroup populations, including Asian vs non-Asian, hepatitis B or C, and regardless of α-fetoprotein (AFP) level. An unplanned analysis revealed a combined OS on both drugs that reached 26 months.[16] Benefit from regorafenib despite being valid, is still an ambiguity. The question is how regorafenib could overcome sorafenib resistance, despite being very similar. It is unknown whether a surge in VEGF and angiogenesis after failure of sorafenib, involvement of other pathways, or altogether can explain its efficacy. A small study investigated the effect of sorafenib beyond first progression, with modest OS benefit (P=0.012).[17] Suppressing angiogenesis beyond progression may have survival benefit on its own; add to it targeting other pathways with regorafenib. Preclinical data suggests that sorafenib treated cell lines express insulin growth factor-1 (IGF-1)[18], so far

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regorafenib spectrum of action does not include IGF pathway. Both sorafenib and regorafenib were shown to be antagonized in vitro by platelet growth factors, suggesting a common escape mechanism.[19] Is regorafenib exclusively efficient after sorafenib failure, in other words, does sorafenib set the stage for it, is a crucial question. It is unknown yet if this effect would be similarly observed in the second line regardless of the first line therapy, namely immunotherapy, or perhaps in the first line. Molecular biomarkers and clinical correlations studies are needed to help elucidate mechanisms of action and resistance, and guide us for potential combination therapies. Ramucirumab, a recombinant IgG1 monoclonal antibody and VEGF receptor-2 antagonist was assessed in advanced HCC following first-line therapy with sorafenib, in a randomized phase III trial. Median OS for the ramucirumab group was 9.2 months (95% CI 8.0-10.6) versus 7.6 months (6.0-9.3) for the placebo group (HR 0.87 [95% CI 0.72-1.05]; P=0.14).[20] In this study, a significant percentage of patients had elevated AFP above 400 ng/ml. In this subgroup, median OS was 7.8 months (95% CI 5.8–9.3) for the ramucirumab group versus 4.2 months (3.7–4.8) for the placebo group.

Molecular classification has shown a unique subclass of HCC with elevated baseline AFP and enriched with growth signaling kinases, such as FGFR3, FGFR4, and IGF2 and its receptor, which might increase VEGF/VEGFR-2 pathway activity. Elevated AFP has been associated with elevated VEGFR expression, increased angiogenesis, and poor prognosis in hepatocellular carcinoma.[21] Currently, a study of ramucirumab versus placebo in patients with elevated AFP is ongoing (REACH-2, NCT02435433).

Cediranib, another pan-VEGFR tyrosine kinase inhibitor, was looked at in a single center phase II study. Eighty nine per cent of patients received prior systemic therapy and 59% received prior sorafenib. Cediranib at 30 mg daily resulted in an estimated 3-month-PFS rate of 77% [60%, 99%]. Median PFS was 5.3 [3.5, 9.7] months, and median OS was 11.7 [7.5–13.6] months.[22] Previous study showed high toxicity and 5.8 months OS when cediranib was given at 45 mg daily.[23] Cediranib was not further explored in larger conclusion generating studies.

Brivanib is a selective dual inhibitor of VEGF and FGF receptors, both implicated in HCC tumorigenesis and angiogenesis. Phase II study including 46 patients revealed a tumor response rate of 4.3%; the disease control rate was 45.7% and median OS was 9.79 months.[24] Following to these results, a phase III study randomized 395 patients with advanced HCC who progressed on/after or were intolerant to sorafenib to receive brivanib 800 mg orally once per day or placebo. Median OS was 9.4 months for brivanib and 8.2 months for placebo (HR, 0.89; 95.8% CI, 0.69 to 1.15; P=0.3307)[25], showing no added benefit from targeting FGF in this particular study.

In agreement with the antiangiogenesis boom, lenvatinib, an oral inhibitor of VEGFR1-3, FGFR1-4, PDGFR-α, RET, and KIT, was explored and is the last agent to mark and eventually reach the angiogenic ceiling. A phase 2 single-arm study including 46 patients was conducted at sites across Japan and Korea. 34% of patients received prior systemic therapy, and only 13% received prior sorafenib. The median time to progression (TTP) was 7.4 months [95% CI: 5.5-9.4]. 17 patients (37%) had partial response and 19 patients (41%) had stable disease (objective response rate (ORR): 37%; disease control rate (DCR): 78%). Median OS was 18.7 months (95% CI: 12.7-25.1). The most common any-grade adverse events were hypertension, palmar-plantar erythrodysesthesia syndrome, decreased appetite, and proteinuria.[26] The impressive results led to the evaluation of lenvatinib in the first line. Indeed, the open-label, phase III trial (NCT01761266), of lenvatinib versus sorafenib, the last to be reported in the multi-kinase antiangiogenic category, has met its primary endpoint of non-inferiority.[27] 954 patients were enrolled, OS was 13.6 months with lenvatinib compared to 12.3 months with sorafenib, HR 0.92 (0.79-1.06). Lenvatinib achieved statistically significant and clinically meaningful improvements in PFS, TTP, and ORR.

TARGETING MET

Accumulating evidence has established the role of the MET receptor tyrosine kinase, encoded by the *MET* proto-oncogene, in tumor development and metastatic progression. Binding of HGF to MET activates primarily the RAS-MAPK and PI3K-AKT signaling pathways. MET is overexpressed in HCC compared with non-tumor liver tissue, with higher MET expression linked to poor prognosis.

Tivantinib is a selective, oral, small-molecule MET inhibitor that preferentially inhibits growth and induces apoptosis in human tumor cell lines expressing MET. A multicenter, randomized, double-blind, placebo-controlled, phase 2 trial was conducted in patients who had progressed on one previous systemic therapy. First impression results were negative with median PFS of 1.5 months (95% CI 1.4–2.7) in the tivantinib group versus 1.4 months (95% CI 1.4–1.5) in the placebo

group (HR 0.67, 95% CI 0.44–1.04; *P*=0.06), and no difference in median OS. However, the subgroup of patients with MET overexpression showed an improvement in median OS from 3.8 (2.1–6.8) to 7.2 months (95% CI 3.9–14.6) (HR 0.38, 95% CI 0.18–0.81; *P*=0.01).[28] This doubling in survival led to the phase III trial (NCT01755767) of tivantinib after sorafenib exclusively in patients with MET-high tumors, defined by ≥2+ in ≥50% of tumor cells by immunohistochemistry. The completed study did not meet its primary endpoint, and tivantinib failed to improve OS or PFS compared to placebo as per recently reported data.[29] Median OS (95% CI) was 8.4 months (6.8-10.0) in tivantinib vs 9.1 months (7.3-10.4) in placebo, HR=0.97 (0.75-1.25), *P*=0.81. Definition of MET overexpression has not been validated so far and might not be as simple as that, taking into consideration intratumoral heterogeneity. At the same time, cabozantinib, an oral potent inhibitor of MET, RET, VEGFR2, and TIE-2, is being evaluated in "all comers" advanced HCC, regardless of MET expression, after failure of prior sorafenib therapy (CELESTIAL). Investigators chose another approach taking advantage of the multiple pathways involved in HCC and the multi targeting ability of the drug. Preclinical experiences have shown that sorafenib resistant mouse models exhibit high levels of activated MET[30], cabozantinib has also activity against AXL-1[31], part of the TAM receptor tyrosine kinase subfamily, involved in tumor growth and migration. In the phase II randomized discontinuation trial, 41 patients who had received at least one prior systemic therapy received cabozantinib 100 mg daily vs placebo. Prior sorafenib use was 51%. PFS reached 4.2 months.[32] The ongoing phase 3 randomized, double-blind, controlled study includes patients regardless of MET expression.[33] The primary endpoint is OS and secondary endpoints are PFS and ORR by RECIST 1.1. The study met its primary endpoint of OS as per recent press release. Final results will be presented at a scientific meeting.

IMMUNOTHERAPY

Preclinical data have indicated that several immunologic mechanisms contribute to HCC development and growth while impairing effective host antitumor immune surveillance.[34] Little is known about programmed death-ligand 1 (PD-L1) expression in HCC; in a retrospective review of 240 patients with HCC, it was shown that PDL-1 was constitutively expressed in HCC tumor specimens, in a focal or scattered manner. Patients with higher expression of PD-L1 by immunohistochemistry had a significantly poorer prognosis than patients with lower expression.[35] In another study 217 HCC patients were evaluated for PDL-1 expression, it was observed in 17% of tumors and ranged from 1% to 30% of positive cells. PD-L1 expression by neoplastic or intratumoral inflammatory cells in HCC was significantly associated with common markers of tumor aggressiveness (high serum AFP levels, satellite nodules, macrovascular invasion, microvascular invasion, and poor differentiation)[36] Several studies are ongoing to evaluate the role of immune checkpoint blockade in HCC, both upfront and after sorafenib, looking into potential role of prior therapy exposure and the ideal positioning of these agents.

A phase 2 study of tremelimumab in patients with advanced HCC with HCV-related cirrhosis with majority of patients failing prior sorafenib established promising activity. Of 17 patients, 3 (17.6%) achieved a partial response and 10 patients (58.8%) had stable disease. The DCR was 76.4%, and clinical benefit was >12 months in approximately one-third of patients. The median time to disease progression was 6.5 months, which is favorable compared with historical controls for this population. Interestingly, clearance of hepatitis C virus was observed among participants, and most common treatment-related adverse event was elevation in transaminases.[37] Segal, et al. reported the preliminary results of MEDI4736 (durvalumab), a human IgG1 monoclonal antibody to PD-L1, found to be tolerable, with lower rates of hepatotoxicity than observed with cytotoxic T-lymphocyte-associated protein (CTLA)-4 blockade in patients with HCC. Of 19 evaluable patients, there were no responders according to RECIST1.1, although 21% of patients achieved disease control at 12 weeks.[38] Tremelimumab and MEDI4736 are being evaluated each as monotherapy and in combination in patients who failed or were intolerant to sorafenib (NCT02519348).

Nivolumab, a fully human IgG4 monoclonal antibody to PD-1, was tested in an HCC-specific phase 1/2 trial. Efficacy was encouraging, with 2 complete responses noted and an overall objective response rate of 19% by RECIST. The OS rate at 12 months was 62% (95% CI, 42%-76%).[39] Final results were recently reported[40], 262 patients were treated (48 patients in the dose-escalation phase and 214 in the dose-expansion phase). During dose escalation, nivolumab showed a manageable safety profile, including acceptable tolerability. 25% of patients had grade 3/4 treatment-related adverse events. Nivolumab 3 mg/kg was chosen for dose expansion. The objective response

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rate was 20% (95% CI 15-26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI 6-28) in the dose-escalation phase. Responses were observed across etiologies, regardless of etiology, tumor PD-L1 expression and sorafenib exposure. Interestingly, preclinical data suggests that low levels of pERK are associated with sorafenib resistance. Mouse and human HCC samples expressing low pERK showed strong inflammatory infiltrating cells and enrichment of intratumoral CD8+ cytotoxic T lymphocytes that express PD-1[41], suggesting that sorafenib resistance may confer better response to immunotherapy, which remains a theory to be verified. Currently, nivolumab is being compared to sorafenib in the first line setting (NCT02576509); while pembrolizumab is being evaluated in patients who failed prior systemic therapy (NCT02658019). These studies might inform us if there is a major difference in immunotherapy activity based on time of administration. Other innovative approaches have been proposed to enhance efficacy of immunotherapy and manipulate the cancer and its microenvironment, such as combining embolization and radiation therapy to immunotherapy, with the idea of stimulating immunogenicity. Safety and efficacy of Y90 radio-embolization with nivolumab is being evaluated currently (NCT02837029).

Other targets are being evaluated in the second line therapy after sorafenib, such as PEGylated arginine deiminase (ADI-PEG 20), a systemic arginine deprivation agent.

Human HCC cells require exogenous arginine for growth, and it has been shown that they are deficient of argininosuccinate synthetase, the urea cycle enzyme required to catalyze the conversion of citrulline to arginine, thus, auxotrophic for arginine. These observations indicated that depletion of circulating arginine might have a potential anti-cancer effect (ADI-PEG 20), was demonstrated to be potentially active and safe in a phase I/II study[42] including 35 patients with HCC. A randomized phase II study was conducted in Taiwan[43] and included 71 patients, with 89% having failed prior therapies. 4 months' disease control rates were 15% for 160 IU/m^2 group, and 16% for 320 IU/m^2 group. Median OS was 7.4 months, and survival appeared to correlate well with the duration of plasma arginine depletion. Another phase II study evaluated ADI-PEG 20 in Asian patients with advanced HCC, 44% had failed previous therapies. There were no objective responders. The DCR and the median OS of the intent-to-treat population were 31.0% (95% confidence interval (CI): 20.5-43.1) and 7.3 (95% CI: 4.7-9.9) months respectively.[44] 80 Caucasian patients with unresectable and metastatic HCC were included in a phase II study, mean survival was 15.8 months.[45] A phase III randomized clinical trial evaluated ADI-PEG 20 in patients who failed prior systemic therapy. Median OS was 7.8 months vs 7.4 months for placebo (P=0.884, HR=1.022 (95% CI: 0.847, 1.233)) and median PFS 2.6 vs 2.6 (P=0.075, HR=1.175 (95% CI: 0.964, 1.432)). Interestingly, patients with arginine depletion for >8 weeks had a median OS of 12.3 months compared to 7.3 months (P=0.0032) for ≤4 weeks. Similarly, patients with citrulline increase for >8 weeks had a median OS of 11.6 months, compared to 3.5 months (P<0.0001) for ≤4 weeks.[46]

ADI-PEG 20 and 5-fluorouracil (FU) both inhibit thymidylate synthase (TS).[47] Arginine deprivation was shown to have additive effect with 5-FU in inhibiting HCC in a xenograft model.[48] ADI-PEG 20 demonstrated synergy with oxaliplatin in inhibiting HCC growth in a xenograft model.[49] An ongoing phase I, open label, dose-escalation study is exploring the combination of FOLFOX and ADI-PEG 20 in HCC and other GI malignancies (NCT02102022). After reaching the MTD, expansion cohort is initiated to further assess toxicity and obtain preliminary estimates of efficacy.

CONCLUSION

Sorafenib is not the only approved therapy in advanced HCC anymore. Benefit remains concrete across etiologies despite likely inferior role in HBV induced HCC. Lenvatinib was shown to be non-inferior to sorafenib and another approved first-line therapy is expected in 2018. Regorafenib and nivolumab are now approved second line therapies in HCC after progression on sorafenib. Cabozantinib is expected to become another second-line option as well. Results from CheckMate-459, now approaching full accrual, are awaited and might change our first-line choice. The enrichment in HCC treatment landscape was long awaited. Lining up or possibly combining these therapies and choosing wisely among them will be the next challenge. Correlative studies are needed to better elucidate clinical and molecular biomarkers, resistance pathways, and inform future treatment strategies.

Authors' contribution

Both authors contributed in the outline of the work and drafting the article. Ghassan Abou-Alfa provided critical revision of the article and final approval to be published.

Conflicts of Interest

The authors have no conflicts to disclose.

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