Current systemic treatment of hepatocellular carcinoma

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SUMMARY

Advanced hepatocellular carcinoma (HCC) has a poor prognosis and limited therapeutic options. Sorafenib (Nexavar®) was the first drug to demonstrate survival benefit. Recently Regorafenib (Stivarga®) proved to be effective as second-line treatment after progression on Sorafenib. Both are only approved in patients with good performance status and preserved liver function. Alternative treatment options with better efficacy and fewer side effects are still an important medical need. Very recently Lenvatinib (Lenvima®) was granted approval as alternative first-line therapy. Cabozantinib and Ramucirumab showed survival benefit compared to placebo, but are not yet available for clinical use. After promising phase I/II trials, phase III studies with other targeted systemic therapies are being performed. Immunotherapy is another challenging research field that is currently being assessed in clinical trials. Nivolumab (Opdivo®) has received accelerated FDA-approval as second-line therapy. Results are further awaited but will influence the care of patients with advanced hepatocellular carcinoma in the near future.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and represents a major global health problem with increasing incidence and significant cancer-related morbidity and mortality. Forty percent of patients have advanced disease related to the tumour characteristics and/or the underlying chronic liver disease. This results in a poor prognosis with expected median survival times of six months, or 25% at one year.[1] Sorafenib (Nexavar®), an oral multi-tyrosine kinase inhibitor was the first Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved drug that demonstrated survival benefit in patients with advanced HCC.[2] However, efficacy is limited and associated with potential negative side effects. Alternative or complementary treatment options are still an important medical need. We aim to review the current systemic therapeutic options for advanced hepatocellular carcinoma with emphasis on recently published results and ongoing phase III trials in this field.

ADVANCED HEPATOCELLULAR CARCINOMA

The recent European guidelines for HCC use the Barcelona Clinic Liver Cancer (BCLC) classification for treatment allocation. This classification system is based on prognostic variables related to tumour burden, severity of underlying liver disease and patient performance status. Patients with very

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TABLE 1. COMPLETED PHASE III TRIALS FIRST-LINE TREATMENT ADVANCED HCC.

	Trial	N	Control	OS	OS control	P value	TTP/ PFS	TTP/PFS control	P value
Sorafenib	SHARP[2]	602	Placebo	10,7	7,9	<0,001	5,5	2,8	<0,001
Sorafenib	Asian[7]	226	Placebo	6,5	4,2	0,014	2,8	1,4	0,0005
Brivanib	BRISK-FL[11]	1150	Sorafenib	9,5	9,9	0,37	4,2	4,1	0,85
Erlotinib +Sorafenib	SEARCH[12]	720	Sorafenib +placebo	9,5	8,5	0,2	3,2	4	0,91
Linifanib	Cainap et al.[13]	1035	Sorafenib	9,1	9,8	1,05	5,4	4	0,001
Sunitinib	SUN1170[14]	1074	Sorafenib	7,9	10,2	0,99	4,1	3,8	0,83
Lenvatinib	REFLECT[15]	954	Sorafenib	13,6	12,3	NA	7,4	3,7	<0,00001

OS: overall survival (months), TTP: time to progression (months), PFS: progression free survival (months), NA: not available.

early and early-stage HCC (BCLC 0 or BCLC A) are potential candidates for curative treatment with surgical resection, ablation or liver transplantation. Transarterial chemo-embolisation (TACE) is recommended for intermediate-stage HCC (BCLC B) when liver function is preserved but lesions are not resectable or beyond the criteria for transplantation. Patients with vascular invasion, extrahepatic spread or cancer-related symptoms and thus advanced-stage HCC (BCLC C) are not good candidates for locoregional therapy. If these patients are in good general condition (ECOG PS 0-2), they can however benefit from systemic therapy. HCC is known as a chemo-resistant tumour type and until 2008 no systemic drug was available for advanced tumour stage although some chemotherapies were used. Sorafenib was the first treatment found to be effective and is since 2008 the standard-of-care. For end-stage disease (BCLC D) with poor liver function and declined performance state (ECOG PS >2) supportive care is preferred.[4,5]

FIRST-LINE TREATMENT

SORAFENIB

Sorafenib (Nexavar®) is an oral multikinase inhibitor that inhibits tumour cell proliferation by targeting the Ras/Raf/MEK/ERK pathway and neoangiogenesis by inhibition of VEGFR-1, VEGFR-2, VEGFR-3 and PDGF receptor-b tyrosine kinases. The results of the SHARP trial led to FDA and EMA approval for the treatment of advanced HCC. The SHARP trial included 602 patients with unresectable advanced HCC (Child-Pugh A and ECOG PS 0-2) without prior systemic treatment. Oral Sorafenib (400 mg twice daily) compared to placebo resulted in better median overall survival (OS) (10,7 *vs.* 7,9 months; HR 0,69; 95% CI: 0,55-0,87; p <0,001) and longer median time to radiological progression (5,5 *vs.* 2,8 months; p <0,001).[2,6] These results have been confirmed irrespective of disease aetiology in the Asian-Pacific population.[7] Recently two observational studies (Insight study and GIDEON trial) investigated the possibility to extend the use of Sorafenib beyond the initial inclusion criteria of the registration trial.[8,9] Currently a RCT phase III study is ongoing to evaluate the safety and efficacy in Child Pugh B patients (NCT01405573). Until further results, guidelines recommend Sorafenib only for patients with well-preserved liver function (Child Pugh A).[4]

Llovet *et al.* stated that treatment with Sorafenib is generally well tolerated with a manageable adverse event profile. The overall incidence of treatment-related adverse events in the SHARP trial was 80%, the majority grade 1 or 2 in severity, mostly diarrhoea, weight loss and hand-foot skin reactions. Dose interruptions due to adverse events (AE) occurred in 44%, dose reductions in 26% and permanent discontinuation of treatment in 11% of patients.[2] However the observational real-life SOFIA trial showed a higher rate and severity of AE. 91% of patients experienced at least one AE of which 45% was grade 3-4 (most frequent fatigue, hand-foot skin syndrome, and diarrhoea). Dose reduction occurred in 54% of patients, mostly because of AE (83% of cases). The treatment needed to be stopped in 40% of patients because of AE and in 16% as result of deterioration of liver function. This more unfavourable outcome might have been influenced by the higher prevalence of Child-Pugh B patients compared with the SHARP trial.[10] Nevertheless side effects are an important limitation to the clinical use of Sorafenib.

Several systemic agents (Brivanib, Linifanib, Sunitinib, and Erlotinib in combination with Sorafenib) have been compared to Sorafenib in phase III trials as alternative first-line

treatment for advanced HCC but did not reach their endpoints (*Table 1*).[11-14]

LENVATINIB

Lenvatinib (Lenvima®) is an oral multikinase inhibitor that targets VEGF receptors 1–3, FGFR 1–4, PDGFRα, and the KIT and RET proto-oncogenes with good outcomes in phase I and II trials.[15,16] The open label phase III REFLECT trial enrolled 954 previously untreated patients with unresectable HCC. Important exclusion criteria were main portal vein invasion and >50% tumour to total liver volume occupancy. The OS for patients treated with Lenvatinib (12 mg or 8 mg once daily) was 13.6 months compared to 12.3 months with Sorafenib (HR: 0.92; 95% CI: 0.79-1.06). Lenvatinib also improved time to progression (TTP) (8.9 months *vs.* 3.7 months) and progression free survival (PFS) (7.4 months *vs.* 3.7 months). The objective response rate (defined by mRECIST) was better for Lenvatinib (24% *vs.* 9.2% on Sorafenib). These results proved non-inferiority and in August, 2018 the EMA approved Lenvatinib as monotherapy for the treatment of advanced or unresectable HCC without prior systemic therapy. Incidence of grade 3 or worse treatment-related AE was higher for Lenvatinib (57%) than Sorafenib (49%). The toxicity profile of the two drugs seem different and the most common any-grade AE for Lenvatinib were hypertension (42%), diarrhoea (39%), decreased appetite (34%), and weight loss (31%). Treatment-related AE led to dose reduction in 37% and withdrawal in 9% of patients.[15]

DONAFENIB

Donafenib an oral multikinase inhibitor that targets Raf kinase and receptor tyrosine kinases, was studied in a phase II trial for patients with unresectable HCC (Child-Pugh class A). All 126 patients received oral Donafenib 200 mg or 300 mg twice daily for several four week cycles. Median TTP was 111 days in 0,2 g group compared with 110 days in 0,3 g group (HR 0.99: 95% CI: 0,62-1,60). At week sixteen partial response was confirmed in 4,8% of patients and stable disease in 41,7%. Both regimens showed similar treatment responses for patients with HCC, but significant adverse events were reported more frequently in the 0,3 g group. The most common AE that led to dose discontinuation or reduction were hand-foot skin reaction in 9.4%, liver dysfunction in 3.8%, and leukopenia in 1.9% of patients.[18] There is currently a phase III trial (NCT02645981) comparing Donafenib with Sorafenib.

NIVOLUMAB

Nivolumab (Opdivo®) is a human immunoglobulin G4 monoclonal antibody that targets the immune checkpoint inhibitor programmed cell death 1 (PD-1). PD-1 suppresses antigen-specific T cell activation through interactions with its ligands. Disrupting the PD-1 immune checkpoint signalling restores the anti-tumour activity of these suppressed T cells.[19] The CheckMate 040 trial is a phase I/II prospective, non-comparative dose study of Nivolumab assessing safety and clinical benefit. Patients had Child-Pugh scores of 7 or less (Child-Pugh A or B7) for the dose-escalation phase and 6 or less (Child-Pugh A) for the dose-expansion phase and ECOG status of one or less. Patients received intravenous Nivolumab 0,1–10 mg/kg every two weeks in the dose-escalation phase (n=48). Nivolumab 3 mg/kg was given every two weeks in the dose-expansion phase (n=214). The study showed an encouraging objective response using mRECIST criteria of 20% (95% CI 15–26) and this within three months in 69% of responders. The six-month OS was 83% (95% CI 78–88) and the nine-month OS 74% (95% CI 67–79). In Sorafenib-naïve patients (n=80), the overall response rate was 23% percent. The disease control rate was 63%. Twenty-five percent of patients in the dose-escalation phase had grade 3 or 4 treatment related adverse events.[19,20]
Cohorts have been added in the study to compare the efficacy of Nivolumab plus Sorafenib and Nivolumab plus Ipilimumab, a CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibitor. Also additional clinical data will be generated for Child-Pugh B subjects. Further results are awaited. In the meantime, a phase III trial with Nivolumab in first-line is initiated as the CheckMate 459 trial (NCT02576509).

SECOND-LINE TREATMENT

REGORAFENIB

Regorafenib (Stivarga®) is an oral multikinase inhibitor (VEGFR1-3, c-KIT, TIE-2, PDGFR-β, FGFR-1, RET, c-RAF, *BRAF*, and p38 MAP kinase) and FDA approved since April 2017 for the treatment of patients with advanced HCC who have been previously treated with Sorafenib. This approval is based on the recently published RESORCE trial which enrolled 573 patients (BCLC stage B/C, Child Pugh A) which were assigned to best supportive care plus oral Regorafenib 160 mg or placebo once daily during week 1-3 of each four-week cycle. Patients intolerant to Sorafenib were not included. Patients must have tolerated Sorafenib at a dose of at least 400 mg/day for at least 20 of the previous 28 days of treatment. Results showed an improved median OS (10,6 *vs.* 7,8 months; HR 0,63; p <0,0001) and median PFS (3,1 *vs.* 1,5 months). Possible drug related adverse events occurred in 93% of patients and led to interruptions or dose reductions in 54% of patients and to discontinuations in 10% of the Regorafenib group. The most common grade 3/4 events were hypertension, hand-foot skin reaction, fatigue, and diarrhoea.[3]

TABLE 2. COMPLETED PHASE III TRIALS SECOND-LINE TREATMENT ADVANCED HEPATOCELLULAR CARCINOMA.

	Trial	N	OS	OS placebo	P value	TTP/ PFS*	TTP/PFS placebo	P value
Brivanib	BRISK-PS[21]	395	9,4	8,2	0,33	4,2	2,7	<0,001
Everolimus	EVOLVE-1[22]	546	7,6	7,3	0,68	3,0	2,6	NA
Ramucirumab	REACH[23]	565	9,2	7,6	0,14	2,8*	2,1	<0,0001
Regorafenib	RESORCE[3]	573	10,6	7,8	<0,0001	3,2	1,5	<0,0001
ADI-PEG 20	POLARIS2009-001[25]	635			NS			
Tivantinib	METIV-HCC[24]	340	8,4	9,1	0,81			
Tivantinib	JET-HCC	190						NS
Cabozantinib	CELESTIAL[26]	707	10,2	8,0	0,005	5,2*	1,9	<0,001

NA: not available, NS: not significant.

Other second-line phase III trials comparing Brivanib, Everolimus, Tivatinib and ADI-PEG20 with placebo after progression on Sorafenib could not demonstrate survival benefit (*Table 2*).[21-24]

RAMUCIRUMAB

Ramucirumab is a recombinant IgG1 monoclonal antibody and VEGFR2 antagonist. Its efficacy and safety as second-line was investigated in the REACH study. There was no benefit in OS. However, a subgroup of patients with a baseline AFP concentration of ≥400 ng/ml showed a significant difference in OS (HR 0,674; 7,8 *vs.* 4,2 months, p=0,006).[23] Therefore only patients with AFP ≥400 ng/ml were enrolled in the REACH-2 phase III study (NCT02435433). According to press release (*http://investor.lilly.com*) in April, 2018 the study met the primary endpoint of OS as well as the secondary endpoint of PFS in HCC patients who were intolerant or had disease progression while on or following treatment with Sorafenib.

CABOZANTINIB

Cabozantinib is an oral dual VEGFR/MET antagonist, Cabozantinib is an oral dual VEGFR/MET antagonist, also inhibiting other receptor tyrosine kinases (RET, KIT, AXL, FLT3). The role of Cabozantinib in HCC has been investigated in a phase II trial. (30) The phase III trial CELESTIAL (NCT01908426) assessed the efficacy of Cabozantinib as second- or third-line treatment. The trial included 760 patients with advanced HCC who received prior Sorafenib (but not restricted by tolerance) and may have received up to two prior systemic cancer therapies for HCC and had adequate liver function. Patients were randomised to receive 60 mg of cabozantinib once daily or placebo. Median OS was 10.2 months with Cabozantinib and 8.0 months with placebo (HR: 0.76; 95% CI: 0.63-0.92; P = 0.005) and the objective response rates were 4% and less than 1%, respectively (P = 0.009). Grade 3 or 4 adverse events occurred in 68% of patients. The most common high-grade AE were palmar–plantar erythrodysesthesia (17%), hypertension (16%), increased AST level (12%), fatigue (10%) and diarrhoea (10%).[26] In May, 2018 the FDA accepted the supplemental new drug application for Cabozantinib as treatment for patients with previously treated advanced HCC.

APATINIB

Apatinib is an oral multi-kinase inhibitor of the VEGFR-2. Most research has been done in advanced gastric or GEJ tumours. In a phase II clinical study of Apatinib as first- line treatment, Chinese patients (n=121) with advanced HCC (Child-Pugh A) received Apatinib 850 mg or 750 mg daily. The median TTP of the 850 mg group and the 750 mg group was 4,2 months and 3,3 months, respectively. The median OS of the two groups was 9,7 months and 9,8 months. The disease control rate was 48,57% for 850 mg group and 37,25% for 750 mg. The most frequently observed drug-related adverse events were hypertension, proteinuria, and hand–foot syndrome.[31,32] The AHELP study is a multicentre, randomised, double-blind, phase III trial (NCT02329860) which evaluates the efficacy and safety of Apatinib in patients with advanced HCC and progression on systemic therapy.

NIVOLUMAB AND PEMBROLIZUMAB

In 2017 the FDA granted accelerated approval to Nivolumab

KEY MESSAGES FOR CLINICAL PRACTICE

1. Sorafenib (Nexavar®, standard dose 400 mg twice daily) was the first approved first-line treatment in advanced HCC. Treatment results in a median overall survival of 10,7 months.

2. The REFLECT trial showed non-inferiority of Lenvatinib (Lenvima®, standard dose: body weight 60 kg: 12 mg, < 60 kg: 8 mg once daily PO) compared to Sorafenib. The drug was recently approved as first-line therapy in advanced or unresectable HCC.

3. Regorafenib (Stivarga®, standard dose 40 mg four times daily PO) is approved as second-line treatment for patients with radiological progression on treatment with Sorafenib.

4. Immunotherapy with Nivolumab (Opdivo®, standard dose 240 mg every 2 weeks IV) is granted accelerated FDA- (but not yet EMA) approval for second-line treatment of advanced HCC.

(Opdivo®) for the treatment of HCC in patients previously treated with Sorafenib. In 2017 the FDA granted accelerated approval to Nivolumab (Opdivo®) for the treatment of HCC in patients previously treated with Sorafenib. This is based on the findings of the CheckMate 040 trial where the cohort of patients with progression on Sorafenib (n=57) were treated with Nivolumab (3 mg/kg intravenously every 2 weeks). El-Khoueiry et al. found in this subgroup a median OS of 13.2 months and objective response rate of 21%. The disease control rate was 61% and the 6-month OS 75%. (19, 20) Pembrolizumab is also an anti-PD-1 antibody. In the phase III KEYNOTE-240 trial (NCT02702401) Pembrolizumab is compared to placebo as second-line therapy for patients with advanced HCC. The KEYNOTE-394 trial (NCT03062358) will be enrolling Asian patients in this setting.

CONCLUSION

Advanced hepatocellular carcinoma has a poor prognosis with few systemic therapeutic options. Sorafenib is since 2008 considered the standard-of-care for BCLC stage C patients with good performance status (ECOG PS 0-2) and preserved liver function (Child Pugh A). Treatment with Sorafenib increases the overall survival by 2.8 months compared to placebo but patients must be selected carefully because of possible side effects. A number of studies suggested that a subset of Child Pugh B patients might also benefit from Sorafenib, but further RCT's have to confirm this. There is still an unmet need for effective alternative systemic treatment options with better tolerance and efficacy. Lenvatinib showed non-inferiority compared to Sorafenib and Regorafenib proved to be effective after radiological progression on Sorafenib. These drugs got EMA- approval in first- and second-line respectively. So far clinical experience is however still limited. A better understanding of the relative efficacy and toxicity of these drugs will be determinative. Until now there are no biomarkers to predict response to treatment or guide clinical practice. There are still several phase III trials assessing the efficacy of other targeted drugs and immunotherapy after promising phase I/II studies. Results of these trials are awaited but will influence the care of patients with advanced HCC in the near future.

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