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Systemic treatment of advanced hepatocellular carcinoma: From disillusions to new horizons

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Abstract Hepatocellular carcinoma (HCC) is an aggressive malignancy, which accounts for a third of all cancer deaths globally each year. The management of patients with HCC is complex, as both the tumour stage and any underlying liver disease must be considered conjointly. Since the approval of sorafenib in advanced HCC, several phase III clinical trials have failed to demonstrate any superiority over sorafenib in the frontline setting, and no agent has been shown to impact outcomes after sorafenib failure. This review will focus on the range of experimental therapeutics for patients with advanced HCC and highlight the successes and failures of these treatments as well as areas for future development. Specifics such as dose limiting toxicity and safety profile in patients with liver dysfunction related to the underlying chronic liver disease should be considered when developing therapies in HCC. Finally, robust validated and reproducible surrogate end-points as well as predictive biomarkers should be defined in future randomised trials.

0. Introduction

Hepatocellular carcinoma (HCC) is the third cause of cancer-related death worldwide [1]. The rim prognosis of HCC is in great part due to the fact that despite the implementation of screening programs targeting at-risk populations (i.e. patients with chronic liver disease) in most developed countries worldwide, many patients diagnosed with HCC (or HCC recurrence) are not amenable to curative-intent treatments. Despite numerous trials investigating various cytotoxic agents alone or in combination, the role of systemic chemotherapy in advanced HCC remains unclear. No drugs either alone or in combination have been shown to do better than doxorubicin, which did not convincingly improve survival over supportive care [2].

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Indeed, in patients with advanced HCC, sorafenib, an orally available tyrosine kinase inhibitor (TKI) targeting – among others – vascular endothelial growth factor (VEGF), the key mediator of angiogenesis, and RAF, remains the only approved systemic therapy since the results of the two Phase III trials SHARP and Asia–Pacific [3,4] (Table 1). The efficacy of sorafenib in HCC is thought to result from the inhibition of VEGF and of the RAS/RAF/MEK/ERK pathway at the level of RAF. Irrespective of the mechanisms of action of sorafenib which remain not fully understood, the observed low objective response rate (ORR) according to response evaluation criteria in solid tumors (RECIST) (<5%) and the median overall survival (OS) of less than 1 year achieved in randomised studies emphasise the need for new treatments in HCC. This review highlights the results from phase three studies assessing molecular-targeting agents as first-line treatment in combination with, or compared to sorafenib, or as second-line therapy after failure of sorafenib, and details several drugs with new targets under evaluation in phase II and III trials as well as biomarker-driven therapeutic strategies.

1. Recent disillusions

1.1. Antiangiogenic agents

As high VEGF expression and increased micro-vessel density have been associated with poor survival, there is a strong rationale for using antiangiogenic agents in HCC [5,6]. BRISK-FL trial was based on the preclinical and promising clinical activity of brivanib, a dual TKI of

Table 1
Randomised phase III clinical trials completed in hepatocellular carcinoma (HCC) in the first- and second-line settings (2007–2014).

Comparison [Reference] (Name, study number)	Treatment line	Patients (*n*)	TTP (in months)	OS (in months)
Sorafenib versus placebo [3] (SHARP, NCT00105443)	1st	Sorafenib ($n = 299$) Placebo ($n = 303$)	5.5 versus 2.8; HR = 0.58 (95% CI, 0.45–0.74); $P < 0.001$	10.7 versus 7.9; HR = 0.69 (95% CI, 0.55–0.87); $P = 0.00058$
Sorafenib versus placebo [4] (Asia–Pacific, NCT00492752)	1st	Sorafenib ($n = 150$) Placebo ($n = 76$)	2.8 versus 1.4; HR = 0.57 (95% CI, 0.42–0.79); $P = 0.0005$	6.5 versus 4.2; HR = 0.68 (95% CI, 0.50–0.93); $P = 0.014$
Brivanib versus sorafenib [9] (BRISK-FL, NCT00858871)	1st	Brivanib ($n = 577$) Sorafenib ($n = 578$)	4.1 versus 4.2; HR = 1.01 (95% CI, 0.88–1.16); $P = 0.8$	9.5 versus 9.9; HR = 1.05 (95% CI, 0.94–1.23); $P = 0.31$
Sunitinib versus sorafenib [13] (SUN, NCT00247676)	1st	Sunitinib ($n = 530$) Sorafenib ($n = 544$)	3.8 versus 4.1; HR = 1.13 (95% CI, 0.98–1.31); $P = 0.16$	7.9 versus 10.2; HR = 1.30 (95% CI, 1.13–1.5); $P = 0.001$
Linifanib versus sorafenib [14] (LIGHT, NCT01009593)	1st	Linifanib ($n = 517$) Sorafenib ($n = 518$)	5.4 versus 4.0; HR = 0.76 (95% CI, 0.64–0.89); $P < 0.001$	9.1 versus 9.8; HR = 1.04 (95% CI, 0.89–1.22); $P =$ NS
Ramucirumab versus placebo [17] (REACH, NCT01140347)	2nd	Ramucirumab ($n = 283$) Placebo ($n = 282$)	3.5 versus 2.6; HR = 0.59 (95% CI, 0.49–0.72); $P = 0.0001$	9.2 versus 7.6; HR = 0.866 (95% CI, 0.72–1.05); $P = 0.14$
Brivanib versus placebo [18] (BRISK-PS, NCT01108705)	2nd	Brivanib ($n = 263$) Placebo ($n = 132$)	4.2 versus 2.7; HR = 0.56 (95% CI, 0.42–0.78); $P = 0.001$	9.4 versus 8.2; HR = 0.89 (95% CI, 0.69–1.15); $P = 0.33$
FOLFOX versus doxorubicin [24] (NCT00471965)	1st	FOLFOX ($n = 184$) Doxorubicin ($n = 187$)	2.93 versus 1.77 (95% CI, 1.6–2.3)*; $P = 001$	6.4 versus 4.9; HR = 0.80 (95% CI, 0.63–1.02); $P = 0.07$
Everolimus versus placebo [47] (EVOLVE-1, NCT01035229)	2nd	Everolimus ($n = 362$) Placebo ($n = 184$)	3.0 versus 2.6; HR = 0.93 (95% CI, 0.75–1.15); P: NA	7.6 versus 7.3; HR = 1.05 (95% CI, 0.86–1.27); $P = 0.67$
Sorafenib + erlotinib versus sorafenib + placebo [52] (SEARCH, NCT00901901)	1st	Sorafenib + erlotinib ($n = 362$) Sorafenib + placebo ($n = 358$)	3.2 versus 4.0; HR = 1.13 (95% CI, 0.94–1.36); $P = 0.91$	9.5 versus 8.5; HR = 0.92 (95% CI, 0.78–1.1); $P = 0.2$

Mo = months; HR = hazard ratio; ns = not significant; OS = overall survival; PFS = progression-free survival; TTP = time to progression; CI = confidence interval.
* PFS.

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