Editorial

Lenvatinib applicability in the therapeutic strategy of patients with hepatocellular carcinoma

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Introduction

The Expert Consensus on the management of lenvatinib tolerance in patients with hepatocellular carcinoma (HCC) was published (1). There, the authors discussed how possibly lenvatinib-related adverse events could be managed in aim to ensure continued lenvatinib therapy at the highest possible dose, and as a result to gain optimal benefit on survival of patients.

In this editorial, the place of lenvatinib in HCC therapeutic strategies as well as its tolerance are reviewed and discussed.

Role of lenvatinib in systemic therapy for hepatocellular carcinoma

Prior to the era of immune-oncology (IO), sorafenib, a multikinase inhibitor (MKI) silencing the activity of targets present in tumor cells (CRAF, BRAF, V600E BRAF, c-KIT, FLT-3) and tumor neo-angiogenesis (CRAF, VEGFR-2 and -3, PDGFR-ß), was the first systemic agent for advanced HCCs (2). Sorafenib has remained for nearly a decade the sole systemic agent for HCC. Indeed, as late as 2017–2018, two other MKIs, regorafenib (inhibiting kinase proteins involved in angiogenesis, carcinogenesis and anti-tumor immunity: VEGFR-1 to 3, TIE2, KIT, RET, RAF-1, BRAF, BRAFV600E, PDGFR, FGFR) (3), and cabozantinib (silencing several tyrosine kinase activity-receptors involved in tumor growth, angiogenesis and metastatic properties: c-MET, VEGFR, AXL, RET, ROS1, TYR03, MER, KIT, TRKB, FLT3, TIE-2) (4), were validated as second line systemic therapy (2L) after failure of sorafenib.

Sorafenib, regorafenib and cabozantinib had demonstrated their superiority versus (*vs.*) placebo in terms of prolonged overall survival (OS) as primary endpoint in these randomized, controlled, prospective phase-3 trials (HR =0.69, 95% CI: 0.55–0.87, P<0.001; HR =0.63, 95% CI: 0.50–0.79, P<0.0001; HR =0.76, 95% CI: 0.63–0.92, P=0.005, respectively). However, these three MKIs did not show any striking anti-tumor activity as shown by the low objective response rates (ORR) assessed per RECIST 1.1 (sorafenib: 2%; regorafenib: 7%; cabozantinib: 4%) (5). Thus, substantial down-staging of HCC tumors were rare and long-term survivors exceptional.

Lenvatinib was the first compound to successfully challenge sorafenib in first line systemic therapy (1L) for HCC. Lenvatinib is another MKI with a spectrum of targets a little different of sorafenib (VEGFR-1 to 3, FGFR-1 to 4, PDGFR-α, RET and KIT). In the phase-3 REFLECT trial, lenvatinib showed non-inferiority versus sorafenib in 1L for HCC (6). While OS was not significantly different between the lenvatinib and sorafenib arms (13.6 *vs.*

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12.3 months, HR =0.92, 95% CI: 0.79–1.06) reaching the criteria of non-inferiority, lenvatinib showed the strongest tumoricid activity as shown by higher ORR (18.8% *vs.* 6.5% per RECIST 1.1, and 40.6% *vs.* 12.4% per mRECIST) by independent review facility. For the first time was available a MKI potentially able to lead to HCC tumor shrinkage in a significant percentage of patients. As HCC is a tumor with highly multidisciplinary approach for the establishment of therapeutic strategies, it's easily conceivable that the tumoricid activity of lenvatinib for HCC tumors initially ineligible for potentially curative options, might change the strategy and allow some of these patients to finally benefit from potential curative options and prolonged survival. However, this concept, although very exciting, is still unproved and remains to be demonstrated in controlled trials.

The development of IO based on immune checkpoint inhibitors (ICI) has revolutionized the therapeutic paradigm of HCC. Although the monotherapies with PD-1 inhibitors did not show significant benefit in phase-3 trials either in 1L with nivolumab (7) or in 2L with pembrolizumab (8), a significant percentage of long-term survivors was present (9). The data of trials with PD-1 inhibitors for HCC tend to show that ORR could be a reliable surrogate marker on the outcome of patients as shown in the phase 1–2 trial with nivolumab, but however remains to be confirmed in the phase-3 trials (10). So far, two IO-based combinations have shown a significant benefit *vs.* sorafenib: either the combination of PD-L1 (atezolizumab) and VEGF (bevacizumab) inhibitors (ATEZO/BEV), or the combination of PD-L1 (durvalumab) and CTLA-4 (tremelimumab) inhibitors (STRIDE), in the IMbrave-150 (11,12) and HIMALAYA (13) phase-3 trials, respectively. In IMbrave-150, ATEZO/BEV improved OS *vs.* sorafenib (19.2 *vs.* 13.4 months, HR =0.66, 95% CI: 0.52–0.85; descriptive P<0.001) with 30% (95% CI: 0.25–0.35) ORR per RECIST 1.1. In HIMALAYA, STRIDE improved OS *vs.* sorafenib (16.4 *vs.* 13.8 months, HR =0.78, 95% CI: 0.65–0.92, P=0.0035) with 20.1% ORR.

The two IO-based combinations in phase-3 trials assessing the addition of a MKI to a PD-1/PD-L1 inhibitor in COSMIC-312 (14) and LEAP-002 (15) failed to show superiority versus the control arm on OS. In COSMIC-312, atezolizumab plus cabozantinib (ATEZO/CABO) did not improve OS versus sorafenib (15.4 *vs.* 15.5 months, HR =0.90, 95% CI: 0.69–1.18; P=0.44) with a low 11% (95% CI: 8.1–14.0%) ORR. In LEAP-002, pembrolizumab plus lenvatinib (PEMBRO/LENVA) did not significantly improve OS versus lenvatinib monotherapy as control arm (21.2 *vs.* 19.0 months, HR =0.84, 95% CI: 0.71–0.997, P=0.0227 that did not reach the pre-specified threshold of 0.0185) with 26.1% ORR.

Although data should not be compared from one phase-3 trial to another, it is noticeable that among the four IO-based combinations in phase-3 trials cited above, the IO-based combination showing the highest median OS is PEMBRO/LENVA. Further, lenvatinib monotherapy seemed to be stronger than the other control arms with sorafenib in terms of OS (19.0 months for lenvatinib *vs.* 13.4–15.5 months for sorafenib) as well as ORR (17.5% for lenvatinib *vs.* 5.1–11% for sorafenib). These encouraging data of the combination of lenvatinib plus PD-1 inhibitors were found as well in real-world setting of a HCC Chinese population harboring a heterogeneity in general status (ECOG PS 0 to 2) and liver functions (Child-Pugh A and B) (16). Globally, OS was 17.8 months (95% CI: 14.0–21.6) with ORR at 19.6% (95% CI: 15.6–23.6%).

Lenvatinib-related adverse events and recommendations for their management

Although the tolerance of sorafenib, regorafenib or cabozantinib is quite similar (17), in the REFLECT trial lenvatinib showed numerous similarities with sorafenib, but some important treatment-related adverse events (TRAE) of grade 3–4 and significantly different between lenvatinib and sorafenib were: arterial hypertension (23% *vs.* 14%), anorexia (5% *vs.* 1%), loss of weight (8% *vs.* 3%), hand-foot skin reaction (3% *vs.* 11%), and proteinuria (6% *vs.* 2%). Regarding quality of life, the EORTC-QLQ-C30 and EORTC QLQ-HCC18 scores were worsened in both arms. Although time to deterioration of quality of life was earlier in the sorafenib arm for some parameters only, it was globally similar between arms (6).

In LEAP-002, the rate of TRAE of grade 3–4 was 56.7% in the lenvatinib arm and 61.5% in PEMBRO/LENVA, leading to discontinuation of treatment in 10.6% and 18% only, respectively (15). In real-world setting from a Chinese population of 378 patients treated by lenvatinib plus PD-1 inhibitors, data were quite similar, showing 57.9% TRAE of grade 3–4, but higher rate of treatment discontinuation (24.6%). The most frequent grade 3–4 TRAEs were arterial hypertension (15.1%), increased blood bilirubin levels (8.5%), fatigue (7.7%), proteinuria (7.1%), decreased platelet count (6.9%), decreased appetite (6.3%), hypokalemia (6.3%), and diarrhea (5.8%) (16).

Conclusions

All these data tend to suggest that lenvatinib is a highly efficient MKI in the treatment of HCC, and thus the control of its administration through the management of the potential adverse events, as nicely described in the Expert Consensus Review Article (Kim 2022), is of prominent importance to reach the best anticancerous activity.

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