Editorial Commentary

Lenvatinib in elderly hepatocellular carcinoma patients, a new therapeutic option in first line

Gael S. Roth[1,2,3], Bleuenn Brusset[1,2,3], Thomas Decaens[1,2,3]

[1]Faculté de médecine, Université Grenoble Alpes, Grenoble, France; [2]Clinique Universitaire d'Hépato-gastroentérologie, Pôle Digidune, CHU Grenoble, France; [3]Institute for advanced biosciences-INSERM U1209/CNRS UMR 5309/Université de Grenoble-Alpes, Grenoble, France

Correspondence to: Thomas Decaens. Faculté de médecine, Université Grenoble Alpes, Grenoble, France; Clinique Universitaire d'Hépato-gastroentérologie, Pôle Digidune, CHU Grenoble, France; Institute for advanced biosciences - INSERM U1209 / CNRS UMR 5309 / Université de Grenoble-Alpes, Grenoble, France. Email: tdecaens@chu-grenoble.fr.

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Liver cancer is the second leading cause of cancer-related death with approximately 750,000 new cases of hepatocellular carcinoma (HCC) per year worldwide (1). The diagnosis remains late and only 30% of patients have access to curative treatment at the time of diagnosis (2,3). In palliative setting, until recently, only Sorafenib, a multi-tyrosine kinase inhibitor, was validated in first line. Sorafenib allows an overall survival of 10.7 versus 7.9 months with placebo since the SHARP study in 2008 (4). Since then, multiple therapies have failed in first line phase 3 trials versus sorafenib. In 2018, Lenvatinib, another multi-tyrosine kinase inhibitor targeting VEGF receptors 1-3, FGF receptors 1–4, PDGF receptor α, RET, and KIT, showed promising results in a non-inferiority phase 3 trial (5). Lenvatinib met non-inferiority criteria with a median survival time of 13.6 months compared to 12.3 months with sorafenib (hazard ratio 0.92, 95% CI, 0.79–1.06). The most common adverse events with lenvatinib were hypertension (42%), diarrhoea (39%), anorexia (34%), and loss of weight (31%). This toxicity profile seems to be more tolerable compared to sorafenib one from a patient perspective. Second line treatments are approved after intolerance and/or progression under Sorafenib. Lenvatinib is thus a good option in first line treatment of advanced HCC.

Nowadays, hepatocellular carcinoma incidence is constantly increasing as well as worldwide population age, suggesting that treatment of HCC elderly patients constitutes a major public health issue. However, few data are available in phase 3 trials concerning this fragile population as illustrated by the recent non-inferiority phase 3 assessing lenvatinib, where only 13% of patient were older than 75. In an original retrospective study published in Hepatology Research, Tada *et al.* showed that lenvatinib can be used safely and efficaciously in a cohort of HCC patients composed of 50 elderly patients (>75 years) and 50 non elderly patients using propensity score. In this work, lenvatinib showed comparable progression free survival and overall survival regardless of patients' age, as well as similar safety profile. Most frequent adverse events of any grade in elderly patients were fatigue (36.0%), anorexia (26.0%), hypothyroidism (24.0%), proteinuria (22.0%), palmar-plantar erythrodysesthesia (22.0%), and hypertension (20.0%). Twelve percent of elderly patients experienced grade 3–4 fatigue. Nonetheless, lenvatinib dose was significantly lower in elderly group with only 28% of patients treated at a 12 mg dose versus 64% of non-elderly patients. This lower dose doesn't seem to be related to lower weight because BMI was not significantly lower in elderly population. This suggests that this population needs specific treatment adaptations.

Besides, Tada *et al.* proposed a correlation between occurrence of palmoplantar erythrodysesthesia and a better overall survival. Nonetheless, this type of analyses classically were already controversial in sorafenib cohorts as they suffer from biases such as the duration of exposure, the drug dose and the observance, that constitute parameters influencing both the frequency of this adverse event and the survival. This analysis wonders

specific statistical analysis. Thus, these results should be interpreted with caution, especially in a retrospective study with such small groups.

This study offers interesting safety and efficacy data on lenvatinib in an elderly advanced HCC patients, a frequent population that is rarely represented in clinical trials, at a time where well tolerated and promising therapies such as anti-programmed death (PD)-1 inhibitors failed to prove a benefit in phase 3, letting HCC patients with still very few options in first line.

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