Five years of lenvatinib in hepatocellular carcinoma: are there any predictive and/or prognostic factors?

Mara Persano[a], Andrea Casadei-Gardini[b], Valentina Burgio[c], Mario Scartozzi[a], Stefano Cascinu[b] and Margherita Rimini[c]

[a]Medical Oncology, University Hospital of Cagliari, Milan, Italy; [b]Department of Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute Hospital, Milan, Italy; [c]IRCCS San Raffaele Scientific Institute Hospital, Department of Oncology, Vita-Salute San Raffaele University, Milan, Italy

1. Introduction

Lenvatinib is an oral inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3, fibroblast growth factor receptor (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR) α, RET (REarranged during Transfection), and KIT. It was the first drug approved in 2017 for first-line treatment of hepatocarcinoma (HCC) after 10 years of Sorafenib as exclusive standard of care in this setting. The open-label, multicenter, phase III REFLECT trial demonstrated the non-inferiority of Lenvatinib in overall survival (OS) (13.6 months) compared to standard of care Sorafenib [12.3 months; hazard ratio (HR) 0.92; 95% confidence interval (CI) 0.79–1.06]. Lenvatinib was shown to improve secondary efficacy endpoints in all patient subgroups, including progression-free survival (PFS) (7.4 vs 3.7 months; HR 0.66; 95% CI 0.57–0.77; p < 0.0001), median time to progression (8.9 vs. 3.7 months; HR 0.63; 95% CI 0.53–0.73; p < 0.0001) and objective response rate (ORR) (24,1% vs 9,2%; 95% CI 2.15–4.56; p < 0.0001) [1]. These last outcomes has been proved to be an independent predictor of OS in HCC patients [2]. In 2020, Briggs et al. performed an analysis of OS data from the REFLECT trial to balance the differences which could impact on prognosis highlighted in the two treatment arms, thus including serum alpha-fetoprotein (αFP) levels, etiology of hepatitis, and treatments performed after the first line. After correcting this imbalance, the HR concerning OS was 0.814 (95% CI 0.699–0.948) in favor of Lenvatinib [3]. Numerous small single-arm studies in the real-world setting have confirmed efficacy data highlighted by the REFLECT trial. In particular, ORRs ranging between 29.9% and 53.5% have been reported [4–11].

The therapeutic armamentarium available for HCC treatment-naïve patients has been expanding in recent years. Another recently approved option is the combination of the anti-programmed cell death ligand-1 (PD-L1) Atezolizumab plus the anti-VEGF Bevacizumab [12]. The phase III IMbrave 150 trial showed an advantage in OS (19.2 vs 13.4 months; p < 0.001) and PFS (6.9 vs 4.3 months; p < 0.001) in favor of this combination compared to sorafenib [13]. Furthermore, the final data from the phase III HIMALAYA trial were published. The immunotherapic combination of the anti-PD-L1 Durvalumab plus the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) Tremelimumab was shown to significantly improve OS compared to Sorafenib (16.4 vs 13.8 months; p = 0.0035) in first-line [14]. The results of the phase III COSMIC-312 trial have been recently published, showing a significant advantage in PFS (6.8 vs 4.2 months; p = 0.0012), but not in OS (p = 0.438) of the combination of the tyrosine kinase inhibitor (TKI) Cabozantinib plus Atezolizumab compared to Sorafenib in treatment-naïve HCC patients [15]. After the promising data of the phase Ib study (PFS = 9.3 months; OS = 22 months), we are awaiting results from the phase III LEAP-002 trial comparing anti-PD1 Pembrolizumab plus

Lenvatinib with Lenvatinib plus placebo in the first-line setting [16].

In this scenario, characterized by a rapid improvement of the therapeutic options for advanced HCC patients, the definition of prognostic and predictive factors able to identify patients which are more likely to respond to a treatment rather than another one, and to help clinicians in the decision-making process in clinical practice is becoming an urgent need. In these 5 years of use in real-world setting, a number of studies have been aimed to identify prognostic and predictive factors of Lenvatinib efficacy. In order to choose the most effective therapeutic approach for HCC patients in the first-line situation, it may be helpful to summarize these results in this review [Table 1].

2. Clinical parameters

2.1. *BCLC stage*

Trans-arterial chemoembolization (TACE) represents the standard of care for HCC Barcelona Clinic Liver Cancer (BCLC) B treatment, but this stage includes an extremely heterogeneous population in terms of both tumor burden and liver function. In particular, a subgroup is represented by patients with disease that exceeds the up-to-seven criteria (the B2 sub-stage according to the Kinki classification) in which TACE has so far shown not only to be ineffective but also to worsen hepatic functional reserve [17]. On the other hand, in the REFLECT trial, Lenvatinib showed a high tumor response rate (40.2%) with the maintenance of good liver function in patients with a high tumor burden [1]. In 2019, Kudo et al. published a proof-of-concept trial in which outcome data from 30 patients treated with Lenvatinib and 60 patients treated with TACE were analyzed. All patients were classified as BCLC B2 and had good liver function without evidence of vascular invasion. Patients treated with Lenvatinib had ORR (73.3% vs 33.3%; $p < 0.001$), PFS (16 vs 3 months; $p < 0.001$), and OS (37.9 vs 21.3 months; $p < 0.01$) significantly higher than those initially treated with TACE. Additionally, in terms of liver function and Albumin-Bilirubin (ALBI) score significantly decreased in the TACE group when compared to the Lenvatinib group ($p < 0.01$) [18]. These results are complementary to those of a retrospective study conducted by Shimose and colleagues on 171 intermediate-stage HCC patients defined as refractory to TACE with preserved liver function [Child Pugh (CP) A]. PFS was significantly longer in Lenvatinib group than in both Sorafenib group (HR 0.56; 95% CI 0.36–0.88; $p = 0.01$) and TACE group (HR 0.23; 95% CI 0.15–0.36; $p < 0.001$). The COX regression analysis of this study demonstrated that Lenvatinib treatment ($p < 0.0001$) and disease within the up-to-seven criteria ($p = 0.001$) were the only independent factors for PFS. PFS was longer in patients treated with Lenvatinib, beyond the up-to-seven criteria, and with ALBI 1 (245.2 ± 107.9 days) than in those with ALBI 2 (147.1 ± 78.6 days) [19]. Further confirmation of these results also comes from a first-line real-world study on 385 patients treated with Lenvatinib and 555 patients treated with Sorafenib. The analysis, conducted through the inverse

Table 1. Most important prognostic and predictive factors for lenvatinib therapy.

	Prognostic Value	Predictive Value	References
BCLC STAGE	YES	NO	[7,22,45,46]
EHD	YES	YES	[20,29]
NO VIRAL	YES	YES	[29,33]
HBV	YES	YES	[27,33,42]
CHILD PUGH	YES	NO	[7,9,22,35,53]
ALBI	YES	NO	[10,29,40,41,44,46]
ECOG PS	YES	YES	[7,20,29,35,40,42]
NLR	YES	YES	[29,33,41,42]
ALPHA-FETOPROTEIN	YES	NO	[9,22,29,35,39,41,44,45]
PREVIOUS TACE	NO	YES	[20]
PORTAL VEIN THROMBOSIS	YES	YES	[29,42]
DOSE INTENSITY	YES	NO	[56–58]
ALBUMIN	YES	YES	[42,53]
HFSR	YES	NO	[49]
HYPERTENSION	YES	NO	[48–50]
DIARREA	YES	NO	[48]
HYPOTIROIDISM	YES	NO	[48,52,53]
PROTEINURIA	YES	NO	[48]
APPETITE LOSS	YES	NO	[49,50]
FATIGUE	YES	NO	[49]
LEP	YES	NO	[47,]

ALBI: Albumin-Bilirubin; BCLC: Barcelona Clinic Liver Cancer; EHD: extrahepatic disease; HBV: hepatitis B virus; HFSR: hand-foot skin reaction; LEP: Lenvatinib prognostic index; NLR: neutrophil-lymphocyte ratio; PS: performance status.

probability of treatment weighting (IPTW) methodology to balance the two cohorts, showed a longer survival of Lenvatinib compared to Sorafenib in TACE refractory patients (HR 0.69; 95% C 0.50–0.96), with a good performance status (PS) (HR 0.73; 95% CI 0.54–0.99) or without extrahepatic disease (HR 0.69; 95% CI 0.47–0.98) [20]. In 2021, Shimose and colleagues published the results of a retrospective real-world study of patients with intermediate-stage HCC treated with Lenvatinib. In particular, the data of two groups after propensity score matching (PSM) were compared: 24 patients were treated with Lenvatinib alternating with trans-arterial therapy (in case of tumor vascularity resumed or the appearance of a new lesion) and 24 patients were treated with Lenvatinib without alternating with trans-arterial therapy. Patients in the first group showed a significant advantage in OS (median survival time not reached vs. 16.3 months, p = 0.01). Independent factors for OS in the Cox regression analysis were the alternation of treatments (p = 0.009) and ALBI grade 1 (p = 0.011) [21]. These data were also further confirmed by a multicenter Italian study of 144 patients treated with Sorafenib and 144 treated with Lenvatinib. Better OS (p = 0.0312) and PFS (p = 0.0136) were highlighted in favor of Lenvatinib treatment with respect to Sorafenib in BCLC B patients [22]. Starting from these evidences, the multicenter randomized phase III LAUNCH trial was designed. This study compared first-line treatment with TACE plus Lenvatinib versus Lenvatinib alone in 338 BCLC C patients. The results presented at ASCO GI 2022 showed an advantage in OS (17.8 vs 11.5 months; p < 0.001), PFS (10.6 vs. 6.4 months; p < 0.001) and ORR (54.1% vs. 25.0, p < 0.001) in favor of the combination TACE plus Lenvatinib. The most frequent grade 3 or 4 adverse events (AEs) were hypertransaminasemia and hyperbilirubinemia, with a higher incidence in the combination group (p < 0,001 and p = 0,014, respectively) [23]. Additionally, case reports have been reported in the literature in which Lenvatinib therapy obtained local responses such as to also allow conversion hepatectomy for HCC regressed from BCLC B to BCLC A [24].

In conclusion, these data suggest that patients with BCLC B stage and high tumor burden (beyond the up-to-seven criteria) appear to respond very well to Lenvatinib therapy.

2.2. *Etiology*

With the advent of effective antiviral therapies for Hepatitis B (HBV) and C (HCV) infections and with the increasing prevalence of metabolic syndrome in developed countries, recent years are witnessing a sea change in the etiology of cirrhosis. In fact, the metabolic syndrome is accompanied by an increase in the incidence of cases of cirrhosis linked to nonalcoholic steatohepatitis (NASH) and a consequent increased incidence of HCC linked to this particular etiology [25,26]. In other words two large subgroups of HCC patients could be recognized: those with a viral etiology and those with a non-viral etiology. It has therefore become essential for clinicians to understand which therapies work best in each of these subgroups. The impact of HCC etiology on first-line survival outcomes has been investigated in these 5 years by two meta-analyses. The first one included data from the REFLECT, SHARP, and Asia-Pacific trials and showed there were no differences in HCV patients treated with Sorafenib or Lenvatinib (HR 0.91). Conversely, there was a trend in favor of Lenvatinib compared to Sorafenib in HBV patients (HR 0.82) [27]. The second meta-analysis conducted by Pfister and colleagues included data from three immunotherapy trials: CheckMate 459, KEYNOTE-240, and IMbrave 150. It was found that immunotherapy did not offer a survival advantage in the subgroup of non-viral HCC patients. Furthermore, they demonstrated in NASH mouse models that the immune activity induced by immunotherapy could favor the onset of hepatic carcinogenesis [28]. Regarding the efficacy of Lenvatinib in this subgroup, a large retrospective study collected data from 1232 patients from Japan, Korea, Germany, and Italy. Diagnosis of NASH HCC was associated with both longer OS (22.2 vs 15.1 months; HR 0.69; 95% CI 0.56–0.85; p = 0.0006) and longer PFS (7.5 vs 6.5 months; HR 0.84; 95% CI 0.71–0.99; p = 0.0436). Also in the multivariate analysis, the diagnosis of NASH HCC was an independent favorable prognostic factor for OS (HR 0.64; 95% CI 0.48–0.86; p = 0.0028), together with ALBI grade 1, PS 0, αFP <400 ng/ml, neutrophil-lymphocyte ratio (NLR) <3, absence of portal vein thrombosis or extrahepatic disease [29]. Hiraoka and collaborators also conducted a retrospective study on 530 HCC patients receiving Lenvatinib by dividing them into NASH group (103 patients) and viral/alcohol group (427 patients). PFS was better in the NASH group (9.3 vs 7.5 months, p = 0.012), while the difference in OS was very close to significance probably due to the limited number of NASH patients (20.5 vs 16.9 months, p = 0.057). Furthermore, the diagnosis of NASH was found to be an independent prognostic factor for PFS in Cox analysis (HR 0.763, p = 0.036) [30]. Also, in the Italian study mentioned above, the forest plot showed better OS for Lenvatinib than for Sorafenib in the subgroup of patients diagnosed with NASH (p = 0.0459) [22].

In 2022, Kim et al published a study comparing Atezolizumab plus Bevacizumab and Lenvatinib in a real world setting on 232 patients, without highlighting any difference in OS between viral and non-viral patients. However, Lenvatinib achieved a higher ORR than Atezolizumab plus Bevacizumab in NASH patients (36% vs 10%) [31]. A recently published study on 869 HCC patients showed longer survival in the NASH subgroup for patients treated with Lenvatinib (21.2 months) compared to Atezolizumab plus Bevacizumab (12.2 months; p = 0.0181). In contrast, no difference was found in the non-NASH subgroup [32]. The RELEVANT study, a very recent real-world trial on 1325 patients treated with Lenvatinib, showed an OS of 16.1 months (95% CI 15.2–51.6) and an ORR of 38.5%. In multivariate analysis, NASH etiology was independently associated with good prognosis, while HBsAg positivity and NLR > 3 were associated with poor prognosis [33].

In consideration of recent evidences in retrospective analyses, etiology represents a parameter to be taken into consideration in the choice of first-line therapy in clinical practice. However, we do not yet have prospective data available that allow us to use it as an absolute criterion in the choice of treatment.

2.3. Child pugh and ALBI

The REFLECT trial included only CP A patients. However, a subsequent post hoc analysis of this study analyzed data from 60 Lenvatinib-treated patients who progressed to CP B during the first 8 weeks of treatment and 413 Lenvatinib-treated patients who maintained CP A. ORR was 28.3% (95% CI 16.9–39.7) for CP B patients and 42.9% (95% CI 38.1–47.6) for CP A patients. Survival analyses at week 8 showed OS of 6.8 months (95% CI 2.6–10.3) for CP B patients and 13.3 months (95% CI 11.6–16.1) for CP A patients. AEs ≥ 3 were more frequent in CP B patients (71.7% vs. 54.7%) and led to treatment discontinuation more frequently (18.3% vs. 7.5%). However, Lenvatinib was also a feasible treatment in CP B patients because the median duration of treatment was 3.2 months in this subgroup [34].

In 2019, Ueshima and colleagues highlighted that ALBI grade 1 and CP 5 were predictors of lower frequency of Lenvatinib discontinuations due to AEs. Multivariate analysis of data from 82 patients receiving Lenvatinib in a real-world setting showed that ALBI 1 ($p < 0.005$) and αFP <200 ng/mL ($p < 0.01$) are predictors of high ORR [4]. The impact of liver function on outcomes was also confirmed by two other real-world multicenter studies. The first one, published in 2019, involved 152 patients treated with Lenvatinib. As expected, the prognosis of CP B patients was worse than that of CP A patients ($p < 0.001$). Furthermore, in the multivariate analysis, ALBI ≥ 2b was the only prognostic factor related to death (HR 4,632; 95% CI 1.649–13.02; $p = 0.004$) [11]. The second study, published in 2020, involved 181 HCC patients, including 55 CP B and 126 CP A. ORR was significantly greater ($p = 0.002$) in CP A5 patients (44%) than in those CP A6 (25.5%), B7 (22.2%), and B8 (5.3%). In the multivariate analysis, the only factors associated with OS were CP score (A vs B $p = 0.007$) and BCLC stage (B vs C $p = 0.002$) [8].

The influence of Lenvatinib on the maintenance of CP score in a real-world setting was investigated by Terashima et al. They analyzed data of 45 patients treated with Lenvatinib and 135 patients treated with Sorafenib through PSM analysis. In the multivariate analysis, Lenvatinib (Odds ratio 2.556; $p = 0.033$) and ALBI 1 (Odds ratio 7.120; $p < 0.001$) were the factors associated with the maintenance of CP score after 4 weeks from the start of treatment. Compared to Sorafenib, more patients treated with Lenvatinib maintained or improved their CP score after 4 ($p = 0.048$) and 12 ($p = 0.036$) weeks from the start of treatment [35]. In 2020, another multi-center retrospective study on 110 CP A patients treated in real-world with Lenvatinib showed that the factors favoring the preservation of liver function were: male gender, ALBI 1, CP 5, and early or intermediate BCLC stage. In particular, in the CP 5 subgroup, liver function was more preserved in ALBI 1 patients than in ALBI 2 ($p = 0.009$). Conversely, CP 6 (HR 2.17, 95% CI 1.03–4.55, $p = 0.041$) and thrombocytopenia (HR 2.63, 95% CI 1.25–5.26, $p = 0.010$) were factors favoring ascites' onset following liver function decline [36].

2.4. Alpha-fetoprotein

We have already pointed out that low baseline serum αFP levels (<200 ng/mL) are among the factors favorably related to response to Lenvatinib treatment [4]. The reduction of this marker during therapy has also been shown to be a predictor of response, especially in the early phase of Lenvatinib treatment. This was observed in 2018 by Hiraoka et al. in a real-world study that included 105 HCC patients. In this trial, there was a significant log10 decline in serum αFP levels after the first 4 weeks of treatment in patients who presented disease control such as partial response (PR) or stable disease (SD) ($p < 0.001$) [37]. These observations were subsequently confirmed in two other studies. The first one was conducted in 2019 by Kodama and colleagues who showed that there was a correlation between the decline in serum αFP levels and the response to imaging treatment ($p = 0.02$) [38]. The second study, published in 2020 by Saeki et al., highlighted in the multivariate analysis that the decrease in αFP was an independent factor for response only in patients with high baseline levels (odds ratio 51.839; $p = 0.001$). Conversely, in patients with low baseline αFP levels, the most determining factor for the response was the ALBI score (odds ratio 6.866; $p = 0.039$) [39].

Recently, a retrospective analysis of 46 HBV HCC patients treated with Lenvatinib was published. The authors observed that patients with an early decline in serum αFP levels had better ORR (34.5% vs 6.3%; $p = 0.0349$), disease control rate (DCR) (82.8% vs 50%; $p = 0,0203$) and PFS (13 vs 7 months; $p = 0.028$) compared to patients with no αFP decrease. In multivariate analysis, αFP decline was identified as an independent predictive factor for improved PFS [40].

2.5. NLR

NLR is considered a prognostic factor for response and survival in patients receiving Sorafenib. Regarding Lenvatinib, this has been investigated in two real-world retrospective studies. The first one included 237 HCC patients and revealed in multivariate analysis that NLR ≥ 4 was an independent factor associated with both OS (HR 1.874; 95% CI 1.097–3.119) and PFS (HR 1.897; 95% CI 1.268–2.837). DCR was significantly higher in patients with NLR < 4 than in patients with NLR ≥ 4 (85.5% vs 67.3%; $p = 0.007$) [41]. The second one was a PSM analysis on 92 HCC patients with Sorafenib and 92 with Lenvatinib. Rimini and colleagues highlighted that NLR < 3 (such as normal albuminemia, PS > 0, absence of HCV infection and presence of portal thrombosis) had a prognostic and predictive role in Lenvatinib arm ($p = 0.0041$; HR: 0.45; 95% CI: 0.27–0.75; interaction test: 0.0562) [42].

2.6. Muscle mass and nutritional status

HCC patients are often characterized by an altered nutritional status that can lead to the onset of sarcopenia [43]. Two studies investigated the impact of muscle volume on the safety and efficacy of Lenvatinib. In the first study, published by Uojima et al. in 2020, 100 patients were classified into two groups: low skeletal muscle index (SMI) and high SMI. SMI is a parameter that derives from the computed tomography (CT) measurement of skeletal muscle mass normalized for height expressed in m^2. Low SMI patients had worse outcomes both in terms of OS ($p = 0.021$) and time to treatment failure (TTF) ($p = 0.01$). This was mainly related to the fact that Lenvatinib

was poorly tolerated in these patients resulting in a higher discontinuation rate (p = 0.042) [44]. These data are in line with those of the second study conducted by Hiraoka and colleagues who classified 437 patients into two groups using presarcopenia status as a parameter. The state of presarcopenia was defined using the following formula: psoas muscle area at level of middle of third lumbar vertebra (cm^2)/height $(m)^2$. Cut-off values for men and women were 4.24 and 2.5 cm^2 /m^2, respectively. Patients with presarcopenia had worse OS (p < 0.001) and PFS (p = 0.025). Tolerability was also worse with a higher AEs frequency (43.9% vs 18.2%; p = 0.003). Furthermore, in the multivariate analysis of this study the presence of presarcopenia (HR 1.652; p = 0.042) was among prognostic factors for patients receiving Lenvatinib, together with αFP >400 ng/ml (HR 2.271; p < 0.001) and BCLC C or D (HR 1.625; p = 0.018) [45].

The influence of malnutrition status on Lenvatinib outcomes was investigated using the controlling nutritional status (CONUT) score, which is based on 3 parameters: total cholesterol and albumin serum levels, and lymphocytes number. This correlation was investigated in a study that included 164 patients receiving Lenvatinib: the CONUT score was the most important parameter for OS which was significantly longer in patients with a good nutritional status, i.e. with a CONUT score <5 (not reached vs. 11.3 months; p < 0.001) [46].

Literature data highlighted various possible prognostic and predictive factors implicated in the first-line treatment of HCC patients. Lenvatinib has been shown to obtain better outcomes in patients with preserved liver function (CP A and ALBI 1), with low baseline αFP and NLR levels. Recently, Rapposelli et al. tried to group all the observations published so far in prognostic and predictive terms by applying the technique of recursive partitioning analysis (RPA) on data of 404 patients receiving Lenvatinib. The result was a new prognostic score, the Lenvatinib prognostic index (LEP), which classified patients into low, medium, and high risk based on the following variables: ALBI, BCLC, previous TACE, and prognostic nutritional index (PNI). Low-risk patients (PNI > 43.3 and previous TACE) according to LEP had longer OS than medium- and high-risk patients (29.8 vs 17 vs 8.9 months; p < 0.0001) [47]. These data were also confirmed in a larger validation cohort. The high-risk group effectively identifies the categories of patients who will not have good responses to treatment with lenvatinib, i.e. patients with PNI < 43.3 and ALBI grade 2 and patients with PNI < 43.3, ALBI grade 1 and BCLC C [].

2.7. Adverse events

A post hoc analysis of 478 patients treated with Lenvatinib in the REFLECT trial showed that longer survival was associated with the onset of the most common side effects due to treatment, particularly hypertension (HR 0.64; 95% CI 0.52–0.80; p = 0.00005), diarrhea (HR 0.72; 95% CI 0.58–0.90; p = 0.00314), proteinuria (HR 0.76; 95% CI 0.60–0.98; p = 0.03042), and hypothyroidism (HR 0.72; 95% CI 0.54–0.96; p = 0.02377) [48]. In these 5 years of use of Lenvatinib in clinical practice, the prognostic and predictive value of treatment AEs has been confirmed by several studies in real-world setting. In 2019, Hiraoka and colleagues showed that the onset of hand-foot skin reaction (HFSR) was associated with a longer time to progression (TTP) (not reached vs 8.9 months; p = 0.007) [11]. In 2020, Ohki et al. published the results of a retrospective multicenter study that included 77 patients. In multivariate analysis, AEs associated with worse PFS were: thyroid dysfunction ≥2 (HR 4.57; 95% CI 2.05–10.20; p < 0.01) and appetite loss (HR 3.58; 95% CI 1.72–7.52; p < 0.01) [10]. In the same year, the results of a retrospective study, conducted by Shimose and collaborators on 177 patients, also confirmed what had already been observed. In particular, HFSR (not reached vs. 15.4 months, p = 0.04) and hypertension (not reached vs. 14.4 months, p = 0.01) were associated with a longer median survival time. As for prognosis, hypertension was the earliest predictor of good prognosis; in contrast, appetite loss and fatigue ≥3 were predictors of poor prognosis [49]. The largest cohort (606 Italian and Japanese patients), in which predictive and prognostic value of Lenvatinib AEs was evaluated, was the one analyzed by Rapposelli and colleagues. In this trial, appetite loss ≥2 was predictive of both worse OS (HR 1.70; 95% CI 1.25–2.32; p = 0.0007) and lower PFS (HR 1.36; 95% CI 1.04–1.77; p = 0.0277); conversely, the onset of G2 hypertension (HR 0.66; 95% CI 0.46–0.93; p = 0.0188) was predictive of better OS, while a longer PFS was predicted by the onset of HFSR (HR 0.72; 95% CI 0.56–0.93; p = 0.0149) [50]. Literature data reported hypothyroidism incidence related to Lenvatinib between 16% and 21.7% [1,51]. Hypothyroidism onset in HCC patients during Lenvatinib treatment was specifically investigated in two different retrospective real-world studies and was associated with longer PFS (p < 0.001) and better prognosis (p = 0.026) [52,53].

Shimose's study cited previously also found a higher prevalence of proteinuria (p = 0.01), appetite loss ≥2 (p = 0.01), and fatigue ≥3 (p = 0.04) related to Lenvatinib in >71 years group of patients []. In contrast, the study by Tada et al. showed no difference in elderly HCC patients not only in AEs prevalence but also in survival outcomes [54].

To achieve lower AEs frequency and lower prevalence of treatment discontinuations, an alternative way of administration of Lenvatinib called the weekend-off strategy (5 days on/2 days off) has also been proposed. Compared to standard administration of Lenvatinib, this strategy has been shown to improve therapeutic duration (p < 0.001) and survival (p < 0.05). In addition, it has also been tested in mouse models, with evidence of greater preservation of organs' vascularity involved in AEs. In particular, compared to standard administration, less damage to vascular structures of thyroid and adrenal glands was observed, which is hypothesized to be implicated in the pathogenesis of some common side effects caused by Lenvatinib, including fatigue [55].

In conclusion, AEs such as hypertension and HFSR are associated with better outcomes, as opposed to appetite loss and fatigue.

2.8. Dose intensity

The phase II 202 trial showed that a lower rate of AEs and treatment discontinuations was associated with adjustment of Lenvatinib dosage to body weight [46]. For this reason, in the

REFLECT trial, patients weighing <60 kg received a dose of 8 mg per day, while patients weighing >60 kg received 12 mg per day without impact on survival outcomes, as also demonstrated from a subsequent post hoc analysis [1]. In 2019, three studies were published that investigated relationship between Lenvatinib dose intensity and its efficacy. The first study was conducted by Takahashi and analyzed data from 50 HCC patients thus showing that patients who received ≥75% of the therapy dose at 8 weeks of initiation had a longer PFS (7.4 vs. 3.3 months, p = 0.004) [56]. Instead, Sasaki and colleagues demonstrated on data from 81 patients, that higher relative dose intensity (RDI) were related to higher ORR (p < 0.05), thus resulting in improved OS (p = 0.011) [5]. These results were also confirmed by Eso and colleagues who showed that patients with a higher RDI in relation to body surface area at 2 months from the start of treatment (2 M-DBR) also had better ALBI grade (p = 0.0437) and CONUT score (p = 0.0222). Furthermore, in the multivariate analysis of this study which included 45 patients, 2 M-DBR was the only significant parameter for a higher PFS (p = 0.0001) [57]. These data were also confirmed by three other studies published in 2020. The first one, conducted by Kirino et al. on 48 patients treated with Lenvatinib, found that achieving a RDI ≥ 70% at 4 weeks was associated with higher OS (HR 0.28; 95% CI 0.09–0.90; p = 0.03) and DCR (91,7% vs 54,2%; p = 0.008). This RDI was most readily achieved by patients with adequate albumin levels (>3.4 g/dL or ALBI < - 2.71) [58]. In the multivariate analysis of the study published by Ohki and colleagues on 123 patients, RDI ≥ 70% was an independent factor for a better PFS (HR 0.55; p = 0.025), but not for OS [59]. In a small subsequent study of 21 patients, Hata et al. analyzed the correlation between response to Lenvatinib and its median plasmatic concentration. In particular, patients with high plasmatic concentration (≥42.68 ng/ml) showed higher ORR (80 vs 18.2%; p = 0.0089) [60].

The maintenance of dose intensity during the early stages of treatment with Lenvatinib therefore appears to be a factor capable of influencing therapeutic outcomes.

2.9. Radiological response

Radiological factors have also been identified that can influence the response to Lenvatinib. In particular, a study on 51 HCC patients showed that the heterogeneous enhancement pattern on staging CT scan was an independent positive factor for response to Lenvatinib therapy (odds ratio 4.75, p = 0.042) [61]. Takahashi and colleagues conducted a study on the radiological response obtained during the early phase of Lenvatinib treatment in terms of early tumor shrinkage (ETS) that is defined as the sum of target lesions' longest diameters. In the multivariate analysis of this study on 104 patients, ETS ≥ 10%, CP A5, and absence of macrovascular invasion resulted independent factor for longer OS [62]. Another radiological factor to consider is represented by CT attenuation value (CTav), the role of which has been investigated in patients treated with Lenvatinib who achieved complete response (CR). The authors highlighted that values below 30.2 HU (N30-CTav) were predictive of necrosis resulting from Lenvatinib therapy and that patients with N30-CTav occupancy rate ≥30.6% had lower rate of local recurrence at 1 year (p < 0.001) [63].

Necrosis detectable in reevaluation CT scans appears therefore an early marker of response to Lenvatinib therapy.

3. Biological parameters

Several translational studies investigated the eventual prognostic role of biological parameters, including serum markers, on HCC patients treated with Lenvatinib. The final analysis of 279 patients treated with Lenvatinib and 128 patients treated with Sorafenib in the REFLECT trial showed that elevated baseline serum levels of VEGF, Angiopoietin-2 (ANG2) and FGF21 were associated with poorer prognosis in both arms. In Lenvatinib arm, increased serum levels of FGF19 and FGF23 were observed [64]. In 2020, two studies were published that investigated changes in these potential serum markers during Lenvatinib treatment. In a study on 74 HCC patients receiving Lenvatinib, FGF19 levels (p = 0.0004) and ANG2 levels (p = 0.0002) decreased in responder patients compared to non-responders. The combination of these two markers was found to be predictive of response to Lenvatinib in the multivariate analysis (Odds ratio 9.143; p = 0.0012), showing an association also with PFS (HR 0.171; p = 0.024) [65]. Also, Shigesawa et al. found that only baseline serum levels of FGF19 (p < 0.001) and ANG2 (p = 0.017) were significantly associated with response to Lenvatinib: in particular, low baseline levels were recorded in all patients who showed complete response (CR) or PR [66].

Another biological factor tested was Wisteria floribunda agglutinin (WFA) positive Mac-2-binding protein glycosylation isomer (M2BPGi). In literature, M2BPGi serum levels show a correlation with malnutrition status in HCC patients and are able to predict the risk of liver failure after TACE. A study of 80 patients receiving Lenvatinib showed that low levels of this marker (<1.5 COI) were associated with better RDI (81.5 vs 53.5%; p < 0.0001), ORR (73% vs 30.6%; p = 0.0004), DCR (89.2% vs 38.9%; p < 0.0001) and PFS (p = 0.0003) [67].

Recently, a study published by Myojin and colleagues demonstrated that Lenvatinib eliminated HCC cell lines expressing FGF19 and that Sorafenib eliminated those expressing MET and NRAS. Furthermore, it has been observed that resistance to Lenvatinib therapy in HCC cell lines was determined by down regulation of FGF19 expression, resulting from chronic exposure to the drug. From the analyses carried out on 79 patients undergoing surgery for HCC, it was found that ST6 ß-galactoside α-2,6-sialyltransferase 1 (ST6GAL1) was a protein secreted by cancer cells and whose serum levels increased with the expression of FGF19. Patients with ST6GAL1 high serum levels showed better survival when treated with Lenvatinib than with Sorafenib (p < 0.05) [68]. Another potential factor of resistance to Lenvatinib is represented by ß catenin, which is part of the Wnt signaling pathway. A preclinical study of HCC cell lines showed that interferon regulatory factor (IRF) 2 induced the ß catenin production, thus promoting cell proliferation and inhibiting apoptosis. These factors were overexpressed in cells exposed to Lenvatinib. In particular, increase in IRF2 was correlated with a reduced sensitivity to Lenvatinib, representing

a potential mechanism of resistance on which it could be interesting to intervene to improve therapeutic outcomes [69].

These markers do not currently find application in clinical practice as further validation studies are needed. Indeed, it would be desirable to test noninvasive methods to dynamically monitor these markers during therapy with Lenvatinib.

4. Conclusion

HCC patients are a heterogeneous and frail population whose management can be complex. This complexity is now further increased thanks to the greater therapeutic armamentarium available. The different options available make it necessary to identify the most appropriate therapy for each patient. Further studies will be needed to devise multimodal and sequencing strategies that could eventually change the natural history of these patients.

5. Expert opinion

Up to date, the treatment of hepatocarcinoma has represented a scenario with few perspectives. This was due in part to the inherent complexity and fragility of the patients affected by this pathology. Another important factor to consider is the fact that histological typing is not always necessary for HCC diagnosis. This has contributed to fewer molecular biology studies than has been seen in other cancers. However, what determined most of all the absence of perspectives in past years was the scarcity of therapeutic alternatives, both locoregional and systemic.

Today locoregional treatments foresee a wider range of approaches and systemic treatments have multiplied both in the first line and in the following lines. Another aspect that is changing the history of these patients is the improved clinical management of comorbidities and side effects of treatments. Moreover, a growing awareness about the biological pathways underlying the carcinogenesis process in these patients is gradually opening the way to a personalized medicine even in this oncologic setting. The definition of prognostic and predictive factors able to define patients who are more likely to respond to a treatment rather than another is becoming an urgent clinical need.

Lenvatinib has been shown to obtain better outcomes in patients with preserved liver function (CP A and ALBI 1) and with low baseline αFP levels. This confirms what has also been seen with Sorafenib, namely that systemic therapies offer the best results when used in patients in good general clinical condition. Another particular subgroup that appears to benefit most from Lenvatinib therapy is represented by patients with non-viral cirrhosis. This aspect is of great importance today considering the reduction in cases of viral hepatitis thanks to the new eradicating therapies available and the increase in the prevalence of NASH and non-alcoholic fatty liver disease (NAFLD) associated with the marked spread of the metabolic syndrome. In this particular subgroup of patients, the molecular and genomic study of the tumor microenvironment will be of fundamental importance in the coming years to understand the behavior of this neoplasm and to identify new therapeutic targets. Furthermore, given the spread of these metabolic pathologies in developed countries, these studies could help to set up personalized screening programs for this neoplasm as well.

As for BCLC B patients, TACE is still the standard of care in the guidelines. However, a significant proportion of these patients appear to respond very well to Lenvatinib therapy. In particular, this concerns patients with a high tumor burden (beyond the up-to-seven criteria). Furthermore, Lenvatinib has been shown to be able to achieve responses that lead to disease downstaging and thus allow local treatments, such as TACE and hepatectomy, also in patients with BCLC C HCC. In this setting, it would be interesting to build randomized trials with multimodal neoadjuvant strategies.

The clinical and therapeutic heterogeneity we face today in the management of this pathology must be addressed by trying to identify predictive factors of response to the individual treatments in order to offer each patient the best therapeutic strategy. In addition to this, in the next 5 years it will be essential to design studies that compare different therapeutic sequences with each other. These studies could offer the opportunity to further investigate the molecular and biological behavior of this pathology as has been done in other neoplasms. Only through this knowledge will it be possible to pave the way for precision medicine even for HCC patients.

Funding

The authors have no funding to report.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–1173.
2. Kudo M, Finn RS, Qin S, et al. Analysis of survival and objective response (OR) in patients with hepatocellular carcinoma in a phase III study of lenvatinib (REFLECT). J Clin Oncol. 2019;37(4):186.
3. Ueshima K, Nishida N, Hagiwara S, et al. Impact of baseline ALBI grade on the outcomes of hepatocellular carcinoma patients treated with lenvatinib: a multicenter study. Cancers (Basel). 2019;11:952.

4. Hatanaka T, Kakizaki S, Nagashima T, et al. Analyses of objective response rate, progression-free survival, and adverse events in hepatocellular carcinoma patients treated with lenvatinib: a multicenter retrospective study. Hepatol Res. 2020;50:382–395.
5. Sasaki R, Fukushima M, Haraguchi M, et al. Response to lenvatinib is associated with optimal relativedose intensity in hepatocellular carcinoma: experience in clinical settings. Cancers (Basel). 2019;11:1769.
6. Sho T, Suda G, Ogawa K, et al. Lenvatinib in patients with unresectable hepatocellular carcinoma who do not meet the REFLECT trial eligibility criteria. Hepatol Res. 2020;50:966–977.
7. Ogushi K, Chuma M, Uojima H, et al. Safety and efficacy of lenvatinib treatment in Child-Pugh A and B patients with unresectable hepatocellular carcinoma in clinical practice: a multicenter analysis. Clin Exp Gastroenterol. 2020;13:385–396.
8. Maruta S, Ogasawara S, Ooka Y, et al. Potential of lenvatinib for an expanded indication from the REFLECT trial in patients with advanced hepatocellular carcinoma. Liver Cancer. 2020;9:382–396.
9. Ohki T, Sato K, Kondo M, et al. Impact of adverse events on the progression-free survival of patients with advanced hepatocellular carcinoma treated with lenvatinib: a multicenter retrospective study. Drugs Real World Outcomes. 2020;7:141–149.
10. Hiraoka A, Kumada T, Atsukawa M, et al. Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions—Multicenter analysis. Cancer Med. 2019;8 (8):3719–3728.
11. Briggs A, Daniele B, Dick K, et al. Covariate-adjusted analysis of the Phase 3 REFLECT study of lenvatinib versus sorafenib in the treatment of unresectable hepatocellular carcinoma. Br J Cancer. 2020;122(12):1754–1759.
12. Sho T, Morikawa K, Kubo A, et al. Prospect of lenvatinib for unresectable hepatocellular carcinoma in the new era of systemic chemotherapy. World J Gastrointest Oncol. 2021;13(12):2076–2087.
13. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular Carcinoma. N Engl J Med. 2020;382 (20):1894–1905.
14. A-A GK, George L, Masatoshi K, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM. 2022.
15. Kelley RK, Rimassa L, Cheng A-L, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2022:1–14.
16. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib Study of lenvatinib plus pembrolizumab in uHCC. J Clin Oncol. 2020;38(26):2960–2970.
17. Kudo M, Arizumi T, Ueshima K, et al. Subclassification of BCLC B stage hepatocellular carcinoma and treatment strategies: proposal of modified Bolondi's subclassification (Kinki criteria). Dig Dis. 2015;33:751–758.
18. Kudo M, Ueshima K, Chan S, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and child–pugh A liver function: a proof-of-concept study. Cancers (Basel). 2019;11(8):1084.
• **The present proof-of-concept study demonstrated the benefit derived from Lenvatinib rather than locoregional treatment in intermediate stage HCC which exceed the up to seven criteria**
19. Shimose S, Kawaguchi T, Tanaka M, et al. Lenvatinib prolongs the progression-free survival time of patients with intermediate-stage hepatocellular carcinoma refractory to transarterial chemoembolization: a multicenter cohort study using data mining analysis. Oncol Lett. 2020;20(3):2257–2265.
20. Casadei-Gardini A, Scartozzi M, Tada T, et al. Lenvatinib versus sorafenib in first-line treatment of unresectable hepatocellular carcinoma: an inverse probability of treatment weighting analysis. Liver Int. 2021;00:1–9.
21. Shimose S, Iwamoto H, Tanaka M, et al. Alternating lenvatinib and trans-arterial therapy prolongs overall survival in patients with intermediate stage hepatoCellular carcinoma: a propensity score matching study. Cancers (Basel). 2021;13:160.
22. Burgio V, Iavarone M, Di Costanzo GG, et al. Real-life clinical data of lenvatinib versus sorafenib for unresectable hepatocellular carcinoma in Italy. Cancer Manag Res. 2021;13:9379–9389.
23. Peng Z, Fan W, Zhu B, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment of advanced hepatocellular carcinoma: a phase 3, multicenter, randomized controlled trial. J Clin Oncol. 2022;40(4suppl):380.
24. Tomonari T, Sato Y, Tanaka H, et al. Conversion therapy for unresectable hepatocellular carcinoma after lenvatinib: three case reports. Medicine (Baltimore). 2020;99:42(e22782.
25. Myers S, Neyroud-Caspar I, Spahr L, et al. NAFLD and MAFLD as emerging causes of HCC: a populational study. JHEP Rep. 2021;3 (2):100231.
26. Younossi Z, Stepanova M, Ong JP, et al. Global nonalcoholic steatohepatitis council. nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2019;17(4):748-755.e3.
27. Casadei Gardini A, Puzzoni M, Montagnani F, et al. Profile of lenvatinib in the treatment of hepatocellular carcinoma: design, development, potential place in therapy and network meta-analysis of hepatitis B and hepatitis C in all Phase III trials. Onco Targets Ther. 2019;12:2981–2988.
28. Pfister D, Núñez NG, Pinyol R, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature. 2021;592 (7854):450–456.
•• **The present work is of great interest, since it suggested for the first time a scarce response to immunotherapy in NASH HCC patients**
29. Rimini M, Kudo M, Tada T, et al. Nonalcoholic steatohepatitis in hepatocarcinoma: new insights about its prognostic role in patients treated with lenvatinib. ESMO Open. 2021;6(6):100330.
• **This paper retrospectively highlights a positive prognostic role of NASH etiology in a large cohort of HCC patients treated with Lenvatinib**
30. Hiraoka A, Kumada T, Tada T, et al. Efficacy of lenvatinib for unresectable hepatocellular carcinoma based on background liver disease etiology: multi-center retrospective study. Sci Rep. 2021;11 (1):16663.
31. Kim BK, Cheon J, Kim H, et al. Atezolizumab/Bevacizumab vs. Lenvatinib as first-line therapy for unresectable hepatocellular carcinoma: a real-world, multi-center study. Cancers (Basel). 2022;14 (7):1747.
32. Rimini M, Rimassa L, Ueshima K, et al. Atezolizumab plus bevacizumab versus lenvatinib or sorafenib in non-viral unresectable hepatocellular carcinoma: an international propensity score matching analysis. ESMO Open. 2022;7(6):100591.
33. Casadei-Gardini A, Rimini M, Kudo M, et al. REal life study of LEnVAtiNib therapy for HepAtocellular carcinoma: RELEVANT study. Liver Cancer. 2022. DOI:10.1159/000525145.
34. Huynh J, Cho MT, J-H KE, et al. Post hoc analysis in patients (pts) with unresectable hepatocellular carcinoma (uHCC) who progressed to Child-Pugh B (CPB) liver function in the phase III REFLECT study of lenvatinib (LEN). J Clin Oncol. 2021;39(3):298.
35. Terashima T, Yamashita T, Takata N, et al. Comparative analysis of liver functional reserve during lenvatinib and sorafenib for advanced hepatocellular carcinoma. Hepatol Res. 2020;50 (7):871–884.
36. Hiraoka A, Kumada T, Atsukawa M, et al. Early relative change in hepatic function with lenvatinib for unresectable hepatocellular carcinoma. Oncology. 2019;97(6):334–340.
37. Hiraoka A, Kumada T, Kariyama K, et al. Clinical features of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions: multicenter analysis. Cancer Med. 2019;8:137–146.
38. Kodama K, Kawaoka T, Namba M, et al. Correlation between early tumor marker response and imaging response in patients with advanced hepatocellular carcinoma treated with lenvatinib. Oncology. 2019;97(2):75–81.
39. Saeki I, Yamasaki T, Yamashita S, et al. Early predictors of objective response in patients with hepatocellular carcinoma undergoing lenvatinib treatment. Cancers (Basel). 2020;12(4):779.
40. Liu B, Shang X, Shi J-Y, et al. Early Alpha-fetoprotein response is associated with survival in patients with hbv-related hepatocellular carcinoma receiving lenvatinib. Front Oncol. 2022;12:807189.

41. Tada T, Kumada T, Hiraoka A, et al. Neutrophil–lymphocyte ratio is associated with survival in patients with unresectable hepatocellular carcinoma treated with Lenvatinib. Liver Int. 2020;40(4):968–976.
42. Rimini M, Shimose S, Lonardi S, et al. Lenvatinib versus Sorafenib as first-line treatment in hepatocellular carcinoma: a multi-institutional matched case-control study. Hepatol Res. 2021;51(12):1229–1241.
43. Hiraoka A, Michitaka K, Ueki H, et al. Sarcopenia and two types of presarcopenia in Japanese patients with chronic liver disease. Eur J Gastroenterol Hepatol. 2016;28(8):940–947.
44. Uojima H, Chuma M, Tanaka Y, et al. Skeletal muscle mass influences tolerability and prognosis in hepatocellular carcinoma patients treated with lenvatinib. Liver Cancer. 2020;9(2):193–206.
45. Hiraoka A, Kumada T, Kariyama K, et al. Clinical importance of muscle volume in lenvatinib treatment for hepatocellular carcinoma: analysis adjusted with inverse probability weighting. J Gastroenterol Hepatol. 2021;36(7):1812–1819.
46. Shimose S, Kawaguchi T, Iwamoto H, et al. Controlling nutritional status (conut) score is associated with overall survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib: a multicenter cohort study. Nutrients. 2020;12(4):1076.
47. Rapposelli IG, Shimose S, Kumada T, et al. Identification of lenvatinib prognostic index via recursive partitioning analysis in advanced hepatocellular carcinoma. ESMO Open. 2021;6(4):100190.
48. Rimini M, Kang W, Burgio V, et al. Validation of the easy-to-use lenvatinib prognostic (LEP) index to predict prognosis in advanced hepatocellular carcinoma patients treated with lenvatinib. Hepatol Res. 2022 Dec;52(12):1050-1059. DOI: 10.1111/hepr.13824. Epub 2022 Aug 25. PMID: 35960789.
49. Sung MW, Finn RS, Qin S, et al. Association between overall survival and adverse events with lenvatinib treatment in patients with hepatocellular carcinoma (REFLECT). J Clin Oncol. 2019;37(4):317.
50. Shimose S, Iwamoto H, Niizeki T, et al. Clinical significance of adverse events for patients with unresectable hepatocellular carcinoma treated with lenvatinib: a multicenter retrospective study. Cancers (Basel). 2020;12(7):1867.
51. Rapposelli IG, Tada T, Shimose S, et al. Adverse events as potential predictive factors of activity in patients with advanced hepatocellular carcinoma treated with lenvatinib. Liver Int. 2021;41:2997–3008.
52. Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol. 2017;52:512–519.
53. Koizumi Y, Hirooka M, Hiraoka A, et al. Lenvatinib-induced thyroid abnormalities in unresectable hepatocellular carcinoma. Endocr J. 2019;66(9):787–792.
54. Shomura M, Okabe H, Sato E, et al. Hypothyroidism is a predictive factor for better clinical outcomes in patients with advanced hepatocellular carcinoma undergoing lenvatinib therapy. Cancers (Basel). 2020;12(11):3078.
55. Tada T, Kumada T, Hiraoka A, et al. Safety and efficacy of lenvatinib in elderly patients with unresectable hepatocellular carcinoma: a multicenter analysis with propensity score matching. Hepatol Res. 2020;50(1):75–83.
56. Iwamoto H, Suzuki H, Shimose S, et al. Weekends-off lenvatinib for unresectable hepatocellular carcinoma improves therapeutic response and tolerability toward adverse events. Cancers (Basel). 2020;12(4):1010.
57. Takahashi A, Moriguchi M, Seko Y, et al. Impact of relative dose intensity of early-phase lenvatinib treatment on therapeutic response in hepatocellular carcinoma. Anticancer Res. 2019;39 (9):5149–5156.
58. Eso Y, Nakano S, Mishima M, et al. Dose intensity/body surface area ratio is a novel marker useful for predicting response to lenvatinib against hepatocellular carcinoma. Cancers (Basel). 2019;12(1):49.
59. Pretreatment Heterogeneous Enhancement Pattern of Hepatocellular Carcinoma May Be a Useful New Predictor of Early Response to Lenvatinib and Overall Prognosis
60. Early Tumor Shrinkage as a Predictive Factor for Outcomes in Hepatocellular Carcinoma Patients Treated with Lenvatinib: A Multicenter Analysis
61. Chuma M, Yokoo H, Hiraoka A, et al. Identification of CT values that could be predictive of necrosis (N-CTav) in hepatocellular carcinoma after lenvatinib treatment. Curr Oncol. 2022;29:3259–3271.
62. Ohki T, Sato K, Kondo M, et al. Relationship between outcomes and relative dose intensity of lenvatinib treatment in patients with advanced hepatocellular carcinoma. Anticancer Res. 2019;39 (9):5149–5156.
63. Hata K, Suetsugu K, Egashira N, et al. Association of lenvatinib plasma concentration with clinical efficacy and adverse events in patients with hepatocellular carcinoma. Cancer Chemother Pharmacol. 2020;86(6):803–813.
64. Finn RS, Kudo M, Cheng AL, et al. Final analysis of serum biomarkers in patients (pts) from the phase III study of lenvatinib (LEN) vs sorafenib (SOR) in unresectable hepatocellular carcinoma (uHCC) [REFLECT]. Ann Oncol. 2017;28(5):v605–v649.
65. Chuma M, Uojima H, Numata K, et al. Early changes in circulating FGF19 and ANG-2 levels as possible predictive biomarkers of clinical response to lenvatinib therapy in hepatocellular carcinoma. Cancers (Basel). 2020;12(2):293.
66. Shigesawa T, Suda G, Kimura M, et al. Baseline angiopoietin-2 and FGF19 levels predict treatment response in patients receiving multikinase inhibitors for hepatocellular carcinoma. JGH Open. 2020;4 (5):880–888.
67. Eso Y, Nakano S, Mishima M, et al. Mac-2 binding protein glycosylation isomer predicts tolerability and clinical outcome of lenvatinib therapy for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci . 2021;00:1–10.
68. Myojin Y, Kodama T, Maesaka K, et al. ST6GAL1 is a novel serum biomarker for lenvatinib-susceptible FGF19-driven hepatocellular carcinoma. Clin Cancer Res. 2021;27(4):1150–1161.
69. Guo Y, Xu J, Du Q, et al. IRF2 regulates cellular survival and Lenvatinib-sensitivity of hepatocellular carcinoma (HCC) through regulating ß-catenin. Transl Oncol. 2021;14(6):101059.