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REVIEW

Real-World Effectiveness of First Line Lenvatinib Therapy in Advanced Hepatocellular Carcinoma: Current Insights

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Abstract: Lenvatinib received its initial approval in 2018 for the treatment of advanced hepatocellular carcinoma. It has since emerged as the preferred first line agent, supported by non-inferiority data from the REFLECT trial. Notably, lenvatinib exhibits a more favorable toxicity profile and a higher response rate compared to sorafenib. Despite the approval of immunotherapy in 2020, specifically the combination of atezolizumab and bevacizumab following the IMbrave150 trial, tyrosine kinase inhibitors remain an indispensable class of agents in the landscape of hepatocellular carcinoma treatment. This comprehensive review delves into various facets of lenvatinib utilization in hepatocellular carcinoma, shedding light on real-world data, addressing challenges, and providing insights into strategies to overcome these obstacles.

Keywords: lenvatinib, tyrosine kinase inhibitors, hepatocellular carcinoma, liver cancer, real-world data

Background

Hepatocellular carcinoma (HCC) represents a critical global health burden, ranking among the most prevalent and deadly malignancies. In 2020, approximately 905,000 people were diagnosed with and 830,000 people died from liver cancer, including HCC and intrahepatic cholangiocarcinoma. Overall, HCC represents 70–80% of liver cancers and its incidence varies widely by region, being particularly prevalent in areas with high rates of chronic hepatitis B and C infections, such as East Asia, sub-Saharan Africa, and parts of Southeast Asia.[1–3]

Its etiology is closely related to chronic liver diseases, predominantly viral hepatitis and cirrhosis, highlighting the importance of screening and early intervention. Several staging systems are used to classify HCC, with the Barcelona Clinic Liver Cancer (BCLC) system being one of the most widely accepted. Patients with HCC staged as BCLC B not amenable or refractory to liver directed therapies, as well as BCLC C, are usually referred to systemic treatment.[4]

Disease stage at diagnosis also varies by region: whereas 12% patients in Japan present in BCLC stage C and only 1–2% in terminal stage (BCLC D), between 50% and 60% of HCC patients in North America, Europe, and China present in BCLC stages C and D.[5]

Since sorafenib approval by the US Food and Drug Administration (FDA) in 2007, based on the phase III placebo-controlled SHARP trial, several agents have been approved in the first line setting.[6]

In 2018, lenvatinib was approved by the FDA based on the pivotal, non-inferiority, phase III trial REFLECT, which compared this agent to sorafenib. The results demonstrated the non-inferiority of lenvatinib to sorafenib in terms of overall survival (OS) and progression-free survival (PFS). In addition, lenvatinib showed benefit in terms of the time to progression (TTP), objective response rate (ORR), and tolerance.[7]

Despite recent advances, including the introduction of immune checkpoint inhibitors (ICIs) in the treatment landscape, it is worth mentioning that lenvatinib continues to be a valuable option for patients with HCC and is present in

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most important international guidelines (Table 1). This manuscript provides a comprehensive overview of the current state of knowledge regarding lenvatinib use in this scenario, focusing on real-world data.

Lenvatinib

Lenvatinib is a novel, oral anti-angiogenic multikinase inhibitor. Its targets include vascular endothelial growth factor receptors (VEGFR) 1–3, fibroblast growth factor receptors (FGFR) 1–4, platelet-derived growth factor receptor-α (PDGFR-α), rearranged during transfection (RET) receptor, and c-kit.[13,14]

Several phase I studies have been conducted in patients with solid tumors, exploring different dose levels and schedules. Boss et al, for example, revealed an encouraging anti-tumor activity in melanoma and renal cell carcinoma and a maximum tolerated dose (MTD) of 25 mg daily.[13] Hong et al conducted a 3+3 phase I trial and demonstrated an MTD at 10 mg twice daily for solid tumors; furthermore, pharmacodynamic analysis conducted in a melanoma expansion cohort suggested that several serum biomarkers of apoptosis and angiogenesis could predict clinical outcomes.[14] For example, higher baseline levels of serum cytochrome C and M30, an antibody that recognizes caspase-cleaved cytokeratin-18, were both associated with longer PFS.[14]

Another phase I study was conducted in two centers in Japan, and included only patients with HCC Child–Pugh (CP) A and B. In the CP-A group, the starting dose was 12 mg (50% of the MTD recommended for solid tumors), which was increased to 16 mg in the second level but was not tolerable owing to two dose-limiting toxicities (grade 3 [G3] proteinuria and G3 hepatic encephalopathy) among three patients, and 12 mg was considered the MTD in that population. After the MTD had been evaluated for the CP-A group, the same 12 mg dose was tested in the CP-B group and was found to be not tolerable (G3 increased AST, G3 hyperbilirubinemia and G2 increased creatinine). After reducing the dose to 8 mg, no patient experienced dose-limiting toxicity, and this dose was determined to be the MTD for CP-B patients. Also, the plasma concentration 24 hours after administration (C24 h) for 12 mg once daily was higher in patients with HCC than in patients with other solid tumors at the same dose in a previous phase I study, and comparable to those solid tumor patients taking 25 mg daily. The toxicity of lenvatinib also seems to be affected by CP score, with G3 adverse events (AEs) seen in 11.1% of CP-A patients versus 27.3% in CP-B. The disease control rate, on the other hand, was 66.7% in the CP-A group and 63.6% in the CP-B group.[15]

Table 1 Summary of the Position of Lenvatinib in Current International Guidelines

Guideline	Year	Recommendation	Ref.
NCCN	**2023**	Recommended regimen as first line systemic therapy in Child–Pugh class A advanced HCC patients (with Atezo-Bev and durvalumab plus tremelimumab as preferred regimen)	[8]
		Subsequent line systemic therapy if disease progression	
ASCO	**2020**	First line treatment for Child–Pugh class A and ECOG PS 0–1 patients with advanced HCC where there are contraindications to Atezo-Bev	[9]
		Second line therapy following first line treatment with Atezo-Bev	
ESMO	**2021**	First line systemic option in advanced HCC (while Atezo-Bev regarded as standard)	[10]
		Second line systemic option with progression after Atezo-Bev	
EASL	**2021**	First line systemic treatment for advanced HCC with contraindication to Atezo-Bev	[11]
		Second line systemic therapy after progression of Atezo-Bev	
KLCA-NCC	**2022**	Recommended as first line systemic therapy for Child–Pugh class A ECOG PS 0–1 patients with advanced HCC who are unsuitable for Atezo-Bev and durvalumab plus tremelimumab	[12]
		Considered as second line systemic therapy after failure with Atezo-Bev or durvalumab plus tremelimumab	

Abbreviations: NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; EASL, European Association for the Study of the Liver; KLCA-NCC, Korean Liver Cancer Association–National Cancer Center; HCC, hepatocellular carcinoma; Atezo-Bev, atezolizumab and bevacizumab; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

REFLECT Trial

The REFLECT trial was a pivotal, global, randomized, non-inferiority phase III trial designed to evaluate the safety and efficacy of lenvatinib compared to sorafenib in first line therapy in patients with unresectable or metastatic HCC.[12]

A total of 954 eligible patients were assigned to either lenvatinib (12 mg/day for ≥60 kg body weight or 8 mg/day for <60 kg body weight) or sorafenib (400 mg twice daily) at 154 sites in 20 countries. Lenvatinib demonstrated non-inferiority in OS compared to sorafenib (median OS=13.6 vs 12.3 months, hazard ratio [HR]=0.92, 95% confidence interval [CI] 0.79–1.06), with the predefined upper bound of the 95% CI for non-inferiority being 1.08. Lenvatinib also demonstrated statistically and clinically significant improvements over sorafenib in PFS (7.4 vs 3.7 months, HR=0.66), TTP (8.9 vs 3.7 months), and ORR (24.1% vs 9.2%). Also, radiologic response was predictive of OS regardless of study arm, with OS of 22 months versus 11.4 months comparing responders with non-responders.

Real-World Data

In the past few years, emerging systemic therapies using ICIs have shown encouraging results in most solid tumors. In HCC, combinations of atezolizumab plus bevacizumab and durvalumab plus tremelimumab have demonstrated superiority compared to sorafenib in the IMbrave150 and HIMALAYA phase III trials, respectively.[16,17] Although both combinations have been approved by the FDA for the first line setting, approximately 15–20% of patients will receive tyrosine kinase inhibitors (TKIs) (sorafenib or lenvatinib) in this setting.[18]

Despite well-established selection criteria for orthotopic liver transplantation (OLT), the incidence of recurrence can be as high as 16% of patients.[19]

Because of the risk of rejection, ICI use has been contraindicated in organ transplant recipients. Abdel-Wahab et al published a series of 39 recipients of solid organ transplants treated with ICIs, in which 36% (4/11) of rejections occurred among liver transplant recipients. Overall, the median time between transplant and ICI start was 9 years and the time between ICI and organ rejection was 21 days.[20]

Bang et al conducted a retrospective analysis, which included 45 patients with post-OLT recurrence treated with lenvatinib concomitant to immunosuppressants, including tacrolimus, everolimus, or mycophenolate mofetil (as monotherapy or in combination).[21] The authors demonstrated an ORR of 20%, a median PFS of 7.6 months, and a median OS of 14.5 months. Also, PFS and OS did not differ significantly with the immunosuppressant regimen (everolimus vs others, p=0.384 [PFS] and p=0.480 [OS]), and the safety profile was consistent with the REFLECT trial and other real-world data.[21]

An important barrier to the implementation of any new therapy is access. For example, Abou-Alfa et al revealed that only 10% of providers throughout the African continent had access to lenvatinib and/or atezolizumab plus bevacizumab. Sorafenib was the most common agent available for first line therapy in Africa (66%), and 7% of providers stated that they had limited or no access to therapies owing to the prohibitive cost.[22]

The REFLECT trial randomized approximately 950 patients randomized to sorafenib or lenvatinib, all of whom had preserved liver function (CP-A). Ueshima et al addressed this subject using CP and albumin–bilirubin (ALBI) in a retrospective cohort, and showed that, among patients with CP-A5, ORR was higher in patients with ALBI 1 versus ALBI 2 (57.1% vs 38.5%). Also, the ORR among patients with CP-A6 and CP-B was 28.6% and 0%, respectively.[23]

The ELEVATOR study retrospectively gathered data from 205 patients across 14 centers in Germany and Austria. It compared outcomes between patients who did not meet the inclusion criteria of the REFLECT trial (REFLECT-out) and those who did (REFLECT-in). Despite the inferior outcomes observed in the REFLECT-out group, patients still experienced a notable benefit in terms of median OS (15.6 vs 10.2 months), PFS (8.1 vs 4.8 months), and ORR (25.5% vs 21.1%). However, a higher proportion of these patients had to discontinue therapy owing to deterioration in liver function leading to CP-B cirrhosis compared to patients who met the criteria for REFLECT (20.1% vs 9.1%).[24]

Lenvatinib and the Etiology of Liver Disease

Another subject of debate in the HCC treatment landscape is the impact of the etiology of liver disease as a predictor of the response to a specific therapy. Pfister et al demonstrated, in preclinical models, an aberrant T-cell activation as well as an accumulation of exhausted $CD8^+PD1^+$ T cells in non-alcoholic steatohepatitis (NASH) livers, which could be responsible for the reduced immune surveillance and inferior activity of immunotherapy in this population.[25] Among other experiments, the investigators treated NASH mice bearing HCC with anti-PD1 immunotherapy, and no responses were observed. Also, prophylactic anti-PD1 led to an increase in the incidence of NASH-HCC, which was prevented by the depletion of $CD8^+$ T cells or tumor necrosis factor (TNF) neutralization, suggesting that $CD8^+$ T cells help to induce HCC in this population.[25]

A subgroup analysis conducted in different phase III trials suggests that ICI-based therapy tends to be more effective than TKIs or placebo in patients with underlying viral etiology (HBV and/or HCV) than in those with non-viral etiology.[26] A meta-analysis including 3739 patients with HCC corroborated these data; however, etiology was not associated with worse outcomes among those patients treated with TKIs.[27] The pooled HRs for OS in patients treated with ICIs versus standard of care were 0.64 (95% CI 0.5–0.83) for viral-related HCC and 0.92 (95% CI 0.77–1.11) among non-viral cases. Regarding the impact of etiology in TKI/anti-VEGF therapies, the HRs for OS were 0.81 (95% CI 0.71–0.92) for viral and 0.82 (95% CI 0.67–1.01) in non-viral etiologies.[27]

Furthermore, a retrospective analysis conducted in Japan, which included 67 patients with advanced HCC, showed significantly better PFS (13.7 vs 6.6 months; HR=0.324, 95% CI 0.174–0.602; $p<0.01$) and OS (not evaluable vs 15.9 months; HR=0.277, 95% CI=0.116–0.662; $p<0.01$) in the non-viral group than in the viral HCC group.[28]

In essence, this can be regarded as a hypothesis-generating statement, and further prospective data are required in non-viral populations. This is particularly important considering the heterogeneous nature of this population, which includes NASH, alcoholic cirrhosis, and other unknown etiologies, as well as the different ICI-based therapies available.

Child–Pugh B

Although HCC is a prominent cause of cancer-related mortality globally, there is a deficiency in treatment recommendations specifically tailored to individuals with impaired liver function, such as CP-B patients, and at the same time, real-world data indicate a significant proportion of CP-B patients undergoing lenvatinib therapy.[29]

For instance, Singal et al conducted an analysis involving 233 HCC patients, revealing that 44.6% and 39.1% were categorized as CP-A and CP-B, respectively. These individuals received treatment at diverse healthcare settings, including a tertiary cancer center (45.8%), a private hospital/clinic (35.6%), and an academic teaching hospital (15.3%) in the USA, and the population was more diverse than in the REFLECT trial, with the majority of patients being identified as White or African–American compared with 67% Asian patients in REFLECT.[29] Despite the subjectivity of response assessments in real-world clinical practice, the authors reported PFS at 6 and 12 months of 85% and 64%, and OS at 6 and 12 months of 91% and 72%, respectively.[29]

Ogushi et al assessed the safety and efficacy of lenvatinib in a retrospective analysis including 181 patients (126 were CP-A and 55 CP-B). The ORR was markedly higher in CP-A5 patients (44.0%) than in CP-A6 (25.5%), CP-B7 (22.2%), and CP-B8 patients (5.3%) ($p=0.002$). Median OS at 12 months was also significantly different between CP-A (66.3%) and CP-B patients (30.0%, $p=0.002$).[30]

Furthermore, Huynh et al conducted a post-hoc analysis of patients in the REFLECT trial who progressed to CP-B by week 8 after randomization and compared them to those who remained CP-A. The CP-B group presented inferior ORR (28.3% vs 42.9%), PFS (3.7 vs 6.5 months), and OS (6.8 vs 13.3 months). Also, these patients had a higher incidence of grade ≥3 treatment-related adverse events (TRAEs), as well as drug discontinuation due to TRAEs, compared to the CP-A group (18.3% vs 7.5%).[31]

The LAUNCH trial, a prospective non-randomized study, which recruited in 10 Japanese centers, included 59 patients with HCC, and cirrhosis CP-B, high tumor burden, or in second line therapy. Besides showing lower efficacy, a higher incidence of AEs, and higher treatment discontinuation rates, the investigators found a higher plasma concentration among the CP-B patients, justifying the rationale for assessing a lower dose in future trials.[32]

Overall, these studies suggest that patients with CP-B disease can tolerate treatment but have shorter survival and potentially more AEs than those with CP-A disease, highlighting the fact that this vulnerable population should be considered in future trials with new agents.

Second Line

Immunotherapy has become the established standard first line treatment for a majority of patients with advanced HCC, consequently relegating TKIs to second and subsequent lines of therapy, despite the absence of randomized data supporting this shift. Notably, a recent single-arm phase II trial involving 19 patients who received cabozantinib after progression on atezolizumab plus bevacizumab reported a median OS of 14.3 months.[33] Another, ongoing, phase II trial, REGONEXT, aims to assess the efficacy of regorafenib in a similar treatment scenario.[34]

Persano et al published the first large retrospective multicenter study assessing different TKIs in second line therapy after the IMbrave150 regimen. Among 464 patients treated with IMbrave150, 231 patients did not receive second line treatment (median OS 9.4 months) and 233 received different second line therapies (median OS 15.7 months). Among these treated patients, lenvatinib showed superior OS (17 months, n=84) to sorafenib (14.2 months, n=43) and cabozantinib (12.4 months, n=23).[35]

Another retrospective analysis was performed in China and included 50 patients who had received lenvatinib for second line post-progression to immunotherapy. The investigators showed an ORR of 18%, a median PFS of 5.0 months, and a median OS of 8.5 months. Moreover, prior ICIs combined with anti-angiogenic inhibitors in first line therapy and a PFS ≥6 months at first line were significantly associated with longer OS.[36]

Palmer et al published a retrospective analysis of 53 patients with advanced HCC diagnosed between 2010 and 2021 at the Mayo Clinic, who had received lenvatinib following progression on immunotherapy (85% of them in second line therapy). The authors demonstrated a median PFS of 3.7 months (95% CI 3.2–6.6) and a median OS of 12.8 months (95% CI 6.7–19.5). In this cohort, 62% of patients received atezolizumab and bevacizumab in the first line setting, but no interaction was tested in the univariate or multivariate analyses. In fact, the impact of previous exposure to anti-VEGF on the efficacy of lenvatinib is still not completely understood.[37]

Dose Adjustment

While the standard starting dose of lenvatinib is typically 8 mg or 12 mg daily, according to body weight, the frequent occurrence of AEs leading to dose reduction often restricts its widespread application.

Zhang et al conducted a study wherein a daily starting dose of 4 mg was implemented, with escalation once every 2 weeks in the absence of significant drug-related AEs higher than G2. This approach was compared with the standard-dose strategy of 8 or 12 mg daily, based on body weight. The study found no statistically significant differences in response rate (32.43% vs 42.1%; p=0.335), disease control rate (86.4% vs 84.2%; p=0.686), or PFS (p=0.631). Although no significant difference in G3/4 AEs was observed between the two groups (p=0.083), it is noteworthy that patients in the standard-dose group (36.8%, 7/19) exhibited a numerically higher incidence of G3/4 AEs compared to the dose-escalation group (16.2%, 6/37).[38]

In real-world practice, it is observed that clinicians may initiate lenvatinib at lower doses for specific patients and adjust the dose during treatment based on individual tolerance. Chan et al conducted an analysis examining the impact of the starting dose in 174 patients across six medical centers in China. The study revealed a non-statistically significant difference in OS, with 9.7 months (95% CI 9.0–10.9) being observed in the low-dose group compared to 7.6 months (95% CI 5.6–13.5) in the standard-dose group. Notably, the median OS significantly favored those who underwent dose escalation during treatment (HR=0.31, 95% CI 0.18–0.53; p<0.0001). These data support starting lenvatinib at a lower dose and escalating it later depending on tolerance.[39]

On the other hand, Ikeda et al reported that the peak concentration (C_{max}) and the area under the concentration–time curve (AUC) play a crucial role in determining lenvatinib efficacy. They also observed that reducing the dose of lenvatinib from 12 mg to 8 mg resulted in a 48% decrease in C_{max} and a 45% decrease in AUC.[15]

In a retrospective analysis published by Iwamoto et al, the efficacy and AEs among 135 patients treated with lenvatinib were studied. The investigators also conducted a tolerance and efficacy analysis of a subset of 30 patients treated with the

weekends-off strategy (5 days on/2 days off). Remarkably, weekends-off administration significantly extended the overall administration period and OS ($p<0.001$ and $p<0.05$, respectively). The incidence rates of grade ≥3 AEs were 82.1% and 49.6% in the standard and weekend-off groups, respectively. In addition, a mouse hepatoma model developed in the study indicated that weekends-off administration contributed to the recovery of vascularity in other organs.[40]

LEAP-002 Study

After extensive investigation, robust preclinical data have been presented, suggesting a synergistic effect of combining a multikinase inhibitor such as lenvatinib with an ICI, through modulation of the tumor microenvironment. The LEAP trial program has been developed to evaluate the safety and efficacy of lenvatinib combined with pembrolizumab in different solid tumors.[41–43]

For example, this combination has been approved for patients with advanced endometrial cancer who had previously received at least one platinum-based chemotherapy regimen, based on a phase III study, 309-KEYNOTE-775, which demonstrated significantly longer PFS (7.2 vs 3.8 months; HR=0.56, 95% CI 0.47–0.66; $p<0.001$) and OS (18.3 vs 11.4 months; HR=0.62, 95% CI 0.51–0.75; $p<0.001$) compared to the physician's choice of chemotherapy.[44]

In HCC, LEAP-002 was a phase III trial which enrolled 794 patients with advanced disease in first line therapy to receive oral lenvatinib combined with pembrolizumab or placebo. In the final analysis, after a median follow-up of 17.6 months, median PFS was not statistically significantly increased (8.2 vs 8.0 months; HR=0.867, $p=0.04$, which missed the statistical threshold for PFS of $p=0.002$). Also, after a median follow-up of 32.1 months, median OS was 21.2 months versus 19.0 months (HR=0.840; $p=0.0227$), also missing the statistical threshold of $p=0.0185$. Interestingly, the OS for lenvatinib in the control arm was superior when compared to the REFLECT trial (19 and 13.6 months, respectively), which could, at least in part, contribute to the negative results.[45]

LAUNCH Trial

Transarterial chemoembolization (TACE) is the global standard treatment for BCLC stage B HCC.[5] However, even patients with more extensive disease may benefit from this modality owing to the high burden of liver disease. Also, the embolization induces tumor hypoxia and activates hypoxic response signaling, thereby inducing the upregulation of VEGF and fibroblast growth factor (FGF), both of which are potential targets for TKIs.[46]

Most recently, the phase III LAUNCH trial conducted in China randomized 338 previously untreated patients with BCLC C HCC to lenvatinib plus TACE versus lenvatinib alone. Patients eligible to receive TACE could have a single tumor ≤10 cm or multiple tumors (≤10 foci) with <50% liver involvement. In this study, median OS was the primary endpoint; this reached 17.8 months with the combination compared to 11.5 months with lenvatinib alone (HR=0.45; $p<0.001$), leading to a clinically meaningful 55% reduction in the risk of death. Overall, combined treatment did not cause any unexpected toxicity, with G3/4 AEs being more common with TACE plus lenvatinib than with lenvatinib alone, including alanine transaminase (ALT) elevation (17.6% vs 1.2%; $p<0.001$), aspartate transaminase (AST) elevation (22.9% vs 1.8%; $p<0.001$), and hyperbilirubinemia (9.4% vs 3.0%; $p=0.014$).[47]

Response Prediction

Besides underlying liver disease etiology, different predictors of response have been evaluated, although none of them has been validated in the first line setting with lenvatinib in prospective trials. Saeki et al conducted a retrospective analysis of 99 consecutive patients with HCC treated with lenvatinib, and showed that the alpha-fetoprotein (AFP) response, baseline ALBI score, and change in ALBI score were predictive of radiologic response.[48] Radiomics has also been widely used to predict treatment response in different solid tumors. Bo et al constructed a machine learning model using 25 radiomics features, and were able to predict response in a retrospective cohort including 109 patients with HCC receiving lenvatinib.[49]

Discussion

Lenvatinib plays a prominent role in the management of advanced HCC, and since the REFLECT trial was published it has become preferred over sorafenib owing to its more acceptable toxicity profile, non-inferior OS, and numerically

superior response rate. In clinical practice, however, systemic therapies are frequently administered to patients who do not exactly match the study population of the pivotal trials. Cirrhotic Patients with cirrhosis have a heterogeneous presentation, and at the same time as new TKIs are being developed it is crucial to determine how to apply them in this population with special needs.

Although patients with CP-B disease had inferior OS to those with CP-A disease, this difference is likely to be due to the underlying cirrhosis and does not necessarily reflect a lack of treatment benefit. Previous phase I trials have demonstrated a higher plasma concentration in patients with liver cancer compared to those with other solid tumors, and a higher incidence of G3/4 toxicity events with the 12 mg dose when used in CP-B patients. Having said that, starting with a lower a dose (8 mg) followed by possible dose escalation seems to be a reasonable approach in this vulnerable population. Regarding dose reduction for CP-A patients, despite the lack of studies comparing different regimens, reducing the dose from 12 mg to 8 mg caused a reduction in C_{max} and AUC (concentration–time), by 48% and 45%, respectively. Also, a weekends-off regimen was effective in a retrospective study and is a reasonable option. However, prospective studies comparing lower dose and weekends-off regimens are needed.[13–15]

A challenge commonly seen in HCC treatment is the modest response rate with approved therapies. The LAUNCH trial showed an impressive response rate combining lenvatinib and TACE (54% vs 25% for lenvatinib alone). Curative resection was achieved by 26 patients (15%) in the combination arm because of downstaging, and two patients (2%) achieved a pathologic complete response. Although these data have not been reproduced in the West, this approach could be an interesting option to use as bridging therapy to resection or even to liver transplantation.[47]

Finally, the correlation between underlying liver disease and benefit with different agents remains to be fully explained. The tumor microenvironment in liver cancer is even more complex, given the immunosuppressive nature of this organ. For example, a high-fat diet in mice promotes the recruitment of bone marrow-derived monocytes to the liver, which will be differentiated into anti-inflammatory macrophages through the PPARδ pathway, whereas pro-inflammatory infiltration is seen in mice with NASH.[50] This difference could be explained, for example, by the type of fatty acids to which they are exposed, with saturated fatty acids promoting pro-inflammatory differentiation and unsaturated fatty acids enhancing anti-inflammatory differentiation.[51] Although prospective data are needed to validate this "etiology conundrum", we should also keep in mind that patients may have multiple contributory factors (eg NASH plus viral etiology or NASH plus alcohol), and designing subgroup analyses would be challenging. Having said that, the authors do not endorse any treatment decision based only on underlying liver disease.

Disclosures

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