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Prospect of lenvatinib for unresectable hepatocellular carcinoma in the new era of systemic chemotherapy

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Abstract

The phase III clinical trial of the novel molecular targeted agent (MTA) lenvatinib for patients with advanced hepatocellular carcinoma (HCC) (REFLECT trial) found that lenvatinib was non-inferior to sorafenib in overall survival. Recently, the efficacy of multiple MTAs, including lenvatinib, in practice has been reported, and therapeutic strategies for Barcelona Clinic Liver Cancer (BCLC) intermediate stage HCC are undergoing major changes. Based on these results, lenvatinib could be recommended for patients with transcatheter arterial chemoembolization (TACE)-refractory, ALBI grade 1, within the up-to-seven criteria in the BCLC intermediate stage. Lenvatinib provides a more favorable outcome than TACE, even in cases with large or multinodular HCC beyond the up-to-seven criteria with Child-Pugh grade A. When patients meet the definitions of TACE-refractory or TACE-unsuitable, switching to systemic chemotherapy, including lenvatinib, is for favorable for preserving liver function. If initial treatment, including MTA, has a significant therapeutic effect and downstaging of HCC is obtained, additional TACE or surgical resection should be considered. Lenvatinib also has a therapeutic effect for poorly differentiated type and non-simple nodular type HCC thanks to the survival-prolonging effect of this drug. Furthermore, a significant therapeutic effect is expected in tumors with more than 50% liver involvement or main portal vein invasion, which have traditionally been considered to have a poor prognosis in patients. This suggests that at the start of lenvatinib treatment, HCC patients with ALBI grade 1 may be able to maintain liver functional reserve.

Key Words: Hepatocellular carcinoma; Lenvatinib; Molecular targeted agent; TACE-

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Core Tip: For about 10 years, first-line systemic chemotherapy for patients with advanced hepatocellular carcinoma (HCC) had been limited to sorafenib. The Phase III clinical trial of lenvatinib for patients with advanced HCC showed lenvatinib to be non-inferior to sorafenib with respect to overall survival (OS). The OS of patients is still far from satisfactory, and there is a great unmet medical need for more effective therapies. This review focuses on the current understanding of the therapeutic efficacy and safety of lenvatinib in the world and outlines the role of lenvatinib in the new era of chemotherapy for HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common solid cancers and a major cause of cancer-related deaths globally[1]. According to the Global Cancer Observatory in 2020, HCC is ranked third in mortality, causing over 830000 deaths per year. Despite increasing global incidence as a major cause of cancer death, the development of new anticancer drugs for HCC has been inadequate. Traditionally, HCC has a poor prognosis. However, this might be partly due to the confined treatment options for patients with advanced HCC[2,3].

Since the publication of the practice guidelines of the American Association for the Study of Liver Diseases (AASLD) on the management of HCC in 2005, the Barcelona Clinic Liver Cancer (BCLC) staging system has been widely accepted and is also being used in many clinical trials of new drugs to treat HCC. These take into account factors including tumor burden, liver function, and general health conditions to determine prognosis and the best treatment. Accordingly, patients at an early stage are those with HCC \leq 5 cm or up to three nodules $<$ 3 cm each (BCLC stage A). Patients exceeding these limits, without vascular invasion or extrahepatic spread, fit into the intermediate stage (BCLC stage B). Patients with evidence of a performance status \leq 2 or an aggressive tumor pattern (vascular invasion or extrahepatic spread) correspond to the advanced stage (BCLC stage C)[4].

Systemic chemotherapy is the only therapeutic option for patients with Child-Pugh grade A at BCLC stage B with unresectable HCC and stage C. Prior to the development of the molecular targeted agent (MTA), patients in the advanced stage had a survival time of approximately 6 mo. Systemic chemotherapy for HCC has changed since the introduction of MTA sorafenib in 2007. The SHARP trial demonstrated that sorafenib prolonged median overall survival (OS) compared to placebo in patients who had not received systemic chemotherapy [10.7 mo *vs* 7.9 mo, hazard ratio (HR) = 0.69, 95%CI: 0.55-0.87, $P <$ 0.001][5]. The subsequent Asia-Pacific trial confirmed these results in Asian patients[6]. Therapeutic options for extrahepatic metastases (*e.g.*, lung, lymph node, or bone) and vascular invasion (*e.g.*, portal vein tumor thrombus) have been demonstrated, and relatively long survival has been achieved for patients with BCLC stage C.

However, sorafenib does not shrink or induce necrosis in tumors and has relatively severe adverse events (AEs), including hand-foot-skin reactions. Therefore, the development of a novel MTA that can substitute for sorafenib is much anticipated.

For the past 10 years, sorafenib has been the only available first-line systemic chemotherapy for patients with advanced HCC. Many clinical trials of candidate systemic chemotherapeutic agents for advanced HCC have failed to demonstrate superiority or non-inferiority to sorafenib[7-9]. The phase III clinical trial of the

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lenvatinib for patients with advanced HCC (REFLECT trial)[10] showed lenvatinib to be non-inferior to sorafenib with respect to OS (13.6 mo *vs* 12.3 mo, HR = 0.92, 95%CI: 0.79-1.06). Furthermore, the secondary efficacy endpoints [progression-free survival (PFS) and objective response rate (ORR)] in the lenvatinib group showed a significant improvement compared with sorafenib. Based on the REFLECT trial, lenvatinib has been approved in the United States, European Union, and other countries as a first-line treatment option alongside sorafenib for advanced HCC, making it the first such drug to be used in Japan. A recent Phase III trial (IMbrave150) showed that combination immunotherapy with atezolizumab plus bevacizumab improved outcomes, including OS, PFS, ORR, and disease control rate, compared with sorafenib monotherapy[11]. Based on these results, both the 2020 AASLD and the 2021 European Society for Medical Oncology liver treatment options depends on BCLC staging and treatment guidelines which recommended atezolizumab+bevacizumab as first-line systemic therapy in stage B with transcatheter arterial chemoembolization (TACE)-unsuitable HCC and stage C. In addition, even with the latest version of the treatment algorithm in the Clinical Practice Guidelines for HCC 2020 in Japan, the first-line drug therapy for unresectable HCC is atezolizumab+bevacizumab combination therapy. Sorafenib and lenvatinib, which were previously the first-line treatments, are now second-line treatments. Regorafenib, ramucirumab, and cabozantinib can be used as third-line treatments (Figure 1).

Although various systemic chemotherapies are available for HCC, the OS of patients is still far from satisfactory, and there is a great unmet medical need for more effective therapies. Furthermore, in the future, issues are likely to arise regarding the order and combination of treatment options for HCC.

This review focuses on the current understanding of the therapeutic efficacy and safety of lenvatinib and outlines the role of lenvatinib in the new era of chemotherapy for HCC.

MOLECULAR MECHANISMS OF LENVATINIB

Lenvatinib is an MTA that suppresses vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), proto-oncogene tyrosine-protein kinase receptor RET, platelet-derived growth factor receptor α , and stem cell factor receptor[12]. Because these targets act as drivers in cancer, lenvatinib has been reported to exhibit antitumor and immunomodulatory activities in a variety of preclinical cancer models[13].

Inhibition of the VEGF/VEGFR signaling pathway

Angiogenesis, mostly regulated by the VEGF pathway, is an essential event in tumor growth and metastasis[14]. In particular, VEGFR-2 is a high-affinity VEGF receptor in vascular endothelial cells[15,16]. Ligand binding activates certain signaling pathways, such as the phospholipase-C γ , phosphoinositide 3-kinase (PI3K)/V-akt murine thymoma viral oncogene homolog (AKT) pathways, and rat sarcoma (Ras)/mitogen-activated protein kinase (MAPK)[16]. These signaling pathways have been implicated in endothelial cells and vascular permeability during tumor enlargement[17]. Moreover, VEGFR is highly expressed in HCC cells. Lenvatinib has been shown to inhibit tumor angiogenesis in various preclinical models. In patient-derived and PLC/PRF/5 cell-transplanted tumor models, Lenvatinib administration resulted in a reduction in microvessel density of tumor[18]. In addition, lenvatinib had been found to suppress various types of cancers[19-23], by blocking the VEGFR pathway. These data indicate that lenvatinib exhibits potent anti-angiogenic activity and may have a stronger effect than sorafenib in preclinical models.

Inhibition of the FGF/FGFR signaling pathway

Activated fibroblast growth factor (FGF) signaling can directly facilitate cell proliferation and survival, as well as promote tumor angiogenesis and progression[24]. The binding of FGF to FGFR leads to the activation of the RAS/MAPK and PI3K/AKT signaling pathways[25,26]. FGF and FGFR are typically overexpressed in HCC, and the expression of FGF19/FGFR4 contributes to HCC progression[27]. Analysis of the effects of selective FGFR inhibitors and FGFR small interfering RNAs on cancer stem-like cells (CSCs) in HCC showed that lenvatinib diminished CSCs in HCC by inhibiting FGFR1-3 signaling; however, FGFR4 signaling was not affected. FGF2 and FGF19 are involved in maintaining CD44High/CD133High CSCs in HCC, potentially *via* FGFR1-3[28]. Preclinical studies have shown that lenvatinib inhibits the prolifer-

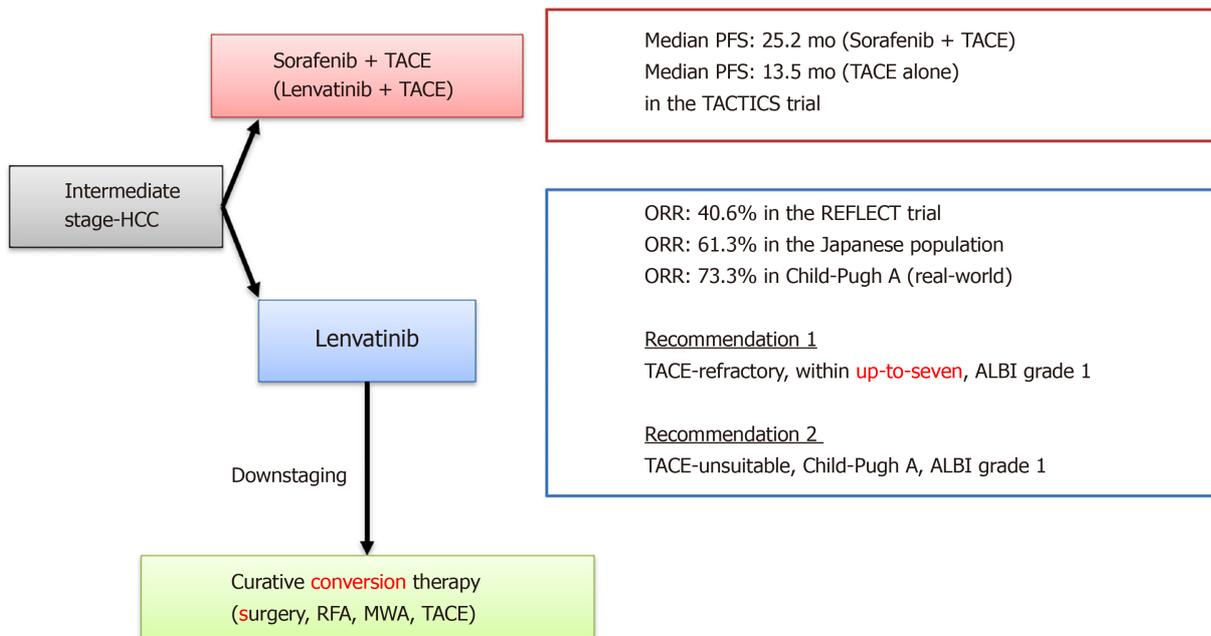


Figure 1 Treatment strategy for intermediate stage hepatocellular carcinoma. HCC: Epatocellular carcinoma; MWA: Microwave ablation; ORR: Objective response rate; PFS: Progression-free survival; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization.

eration of FGF19 and FGFR-overexpressing cell lines[18,28,29].

Inhibition of the RET signaling pathway

RET activates downstream signaling pathways through mutations or chromosome rearrangements, promoting tumor cell growth[30]. The autophosphorylation of specific tyrosine residues of RET allows for the recruitment adaptor proteins that connect the RET receptor to RAS/MAPK and PI3K/AKT signaling pathways, thereby promoting cell growth, proliferation, survival, and differentiation[31]. Lenvatinib can inhibit cell proliferation by blocking RET autophosphorylation[12].

Immunomodulatory activity

The immune escape of tumor cells is the main mechanism of tumorigenesis[32]. It has been suggested that VEGF-A has immunosuppressive properties[33]. VEGF-A produced by tumor cells enhances the expression of immunosuppressive receptors in CD8+ T cells and promotes immune escape[34]. Immune inhibitory receptors cause CD8+ T cell exhaustion by recognizing tumor antigens[32]. Lenvatinib reduced the infiltration of tumor-associated macrophages and increased the percentage of activated CD8+ T cells in HCC[13].

LENVATINIB THERAPY IN INTERMEDIATE STAGE HCC

Efficacy of Lenvatinib in intermediate stage HCC

In recent years, the efficacy of multiple MTAs, including lenvatinib, has been reported. As a result, therapeutic strategies for BCLC intermediate-stage HCC are undergoing major changes. In the REFLECT trial, the ORR of lenvatinib was 40.6% in the mRECIST evaluation, and in the sub-analysis, the ORR of BCLC intermediate stage HCC in the Japanese population was 61.3%[35]. Furthermore, Kudo *et al*[36] reported that a very high response rate (RR) of 73.3% was obtained for Child-Pugh A in BCLC intermediate stage HCC. Tomonari *et al*[37] reported from their real-world data that BCLC intermediate stage HCC cases had fewer AEs, could maintain the dosage amount of lenvatinib, and had a good therapeutic effect. Many reports have demonstrated the high therapeutic effect of lenvatinib in BCLC intermediate stage HCC.

Efficacy of TACE in intermediate stage HCC

TACE is the guideline-recommended standard of care for intermediate stage HCC. The AASLD Consensus Conference showed that locoregional TACE may still be the best approach if the patient's tumor volume is small and nodules can be accessed

superselectively[38]. According to a systematic review of patients treated with lipiodol-based TACE, the survival rates at one, three, and five years were reported to be 70.3%, 40.4%, and 32.4%, respectively, with a median OS of 19.4 mo[39]. But, the efficacy of TACE was not observed equally in all cases. Intermediate-stage HCC varies widely in terms of tumor burden and liver function. The heterogeneity of tumors in the BCLC intermediate stage has led to the development of several prognostic scores, including the Kinki criteria, which are based on liver function and tumor burden that attempt to determine who may obtain the maximum benefit from TACE[40]. The up-to-seven criteria, defined as the sum of the maximum tumor diameter in the liver (cm) and the number of tumors[41], has prognostic value and can predict the recurrence and maintenance of Child-Pugh grade in patients who undergo initial conventional TACE[42]. In intermediate stage HCC, preserving liver function is as important as achieving a high objective response because the treatment goal is to prolong OS. Additional TACE has a lower RR than the initial TACE and increases the risk of liver function loss[43]. Hence, repeated TACE is not recommended, as it leads to decreased liver function and reduced therapeutic efficacy.

Recently, the characteristics of TACE-resistant tumors, which are prone to being TACE-refractory and to exacerbate to Child-Pugh grade B by TACE, have been clarified[36,44]. In cases in which the tumor is a non-simple nodular type, occupying multiple lobes, a large tumor mass, such as beyond the up-to-seven criteria, and of a histopathologically poorly differentiated type, TACE has little effect. As a result, these cases may become TACE-refractory at an early stage[45].

EFFICACY OF LENVATINIB IN TACE-REFRACTORY CASES

Therapeutic alternatives are needed for patients who are TACE-refractory. Repeated TACE could worsen liver function, thereby narrowing the time window for a switch to MTAs, which is recommended for patients with Child-Pugh grade A. In the era of sorafenib, TACE failure/refractoriness was proposed for switching to systemic chemotherapy[46]. The OPTIMIS trial showed that the survival time in TACE-refractory patients was longer in patients who received sorafenib than in those who continued TACE.

A recent study showed that the median PFS times in TACE-refractory patients treated with lenvatinib, sorafenib, and TACE was 5.8, 3.2, and 2.4 mo, respectively [47]. In a Cox regression analysis, lenvatinib treatment and being within the up-to-seven criteria were identified as independent factors for PFS (lenvatinib, $P < 0.0001$; within the up-to-seven criteria, $P = 0.001$). Similarly, decision-tree analysis showed that patients treated with ALBI grade 1 beyond the up-to-seven criteria had longer PFS than patients treated with ALBI grade 2 beyond the up-to-seven criteria. Therefore, lenvatinib could be recommended to patients with TACE-refractory, ALBI grade 1, and within the up-to-seven criteria in the BCLC intermediate stage. Thus, treatment with lenvatinib could give rise to good outcomes in TACE-refractory intermediate-stage HCC patients.

EFFICACY OF LENVATINIB IN TACE-UNSUITABLE CASES

In patients beyond the up-to-seven criteria, TACE treatment was reported to be likely to worsen liver function, potentially resulting in losing the opportunity to be treated with MTA[42,48]. Recently, the Asia-Pacific Primary Liver Cancer Expert (APPLE) consensus statement proposed the criteria for TACE unsuitability[49].

A proof-of-concept study demonstrated that, in patients with intermediate stage HCC who exceeded the up-to-seven criteria, the lenvatinib group showed a significantly higher ORR (73.3% vs 33.3%; $P < 0.001$) and a significantly longer median PFS than the conventional TACE group (16.0 mo vs 3.0 mo; $P < 0.001$)[50]. The ALBI score was maintained in the lenvatinib group during treatment, whereas it worsened in the TACE group. Therefore, in the case of large or multinodular intermediate stage HCC with Child-Pugh grade A, lenvatinib provides a better outcome than TACE.

LENVATINIB AS AN UPFRONT SYSTEMIC CHEMOTHERAPY

When patients meet the definitions of TACE-refractory or TACE-unsuitable, switching

to systemic chemotherapy including lenvatinib may be advisable in order to preserve liver function. Upfront lenvatinib therapy may also be suitable for patients with a high tumor burden or those who are considered TACE-refractory. If the tumor responds well and downstaging is possible with lenvatinib, additional TACE (or surgical resection or ablation) could be considered. However, the efficacy and safety of this strategy have not yet been validated.

Recently, a randomized, controlled trial comparing the efficacy and safety of TACE plus sorafenib to TACE alone (TACTICS trial) found that median PFS was significantly longer in the TACE plus sorafenib group than in the TACE alone group (25.2 mo vs 13.5 mo; $P = 0.006$) [51]. MTA treatment is thought to improve the clinical outcome of TACE by promoting the normalization of tumor vessels and contributing to a higher density of lipiodol deposition [49]. Lenvatinib has a higher RR than sorafenib, suggesting that Len-TACE sequential therapy may be a promising treatment for patients with moderately differentiated HCC.

EFFICACY OF LENVATINIB FOR POORLY DIFFERENTIATED HCC

In the REFLECT study, poorly differentiated HCC was diagnosed in 42 patients (4.4%), with 21 in the lenvatinib group and 21 in the sorafenib group. The ORR was 47.6% in the lenvatinib group and 14.3% in the sorafenib group. Thus, lenvatinib is expected to have an effect on poorly differentiated HCC [49].

HCC shows great diversity of tumor differentiation even in the same nodule, and it is difficult to examine the heterogeneity of all tumors by liver tumor biopsy. Therefore, it is extremely important to evaluate the degree of tumor differentiation using a non-invasive method. Poorly differentiated HCC is characterized by tumors that show a heterogeneous enhancement pattern with irregularly shaped ring structures in the arterial phase of dynamic computed tomography (CT) [52] and tumors in which lesions are detected on FDG-positron emission tomography [53]. Based on the prediction of tumor differentiation by the enhancement pattern of dynamic CT [54], the therapeutic effect of lenvatinib is also recognized for poorly differentiated type and non-simple nodular type, and it has been reported that it has a survival-prolonging effect for all of them [54]. Tumors with a heterogeneous enhancement pattern and irregularly shaped ring structures had an RR of 84%, which was significantly better than the RR of tumors with a homogeneous enhancement pattern, which was 53%. Furthermore, there was no significant difference in the PFS between the two groups. The therapeutic effect of lenvatinib, regardless of the degree of tumor differentiation, will have a significant impact on future HCC treatment [54].

Traditionally, non-simple nodular, poorly differentiated HCC has a poor prognosis with existing treatments, including hepatectomy. In particular, it was difficult to control the progression of poorly differentiated HCC using TACE. Therefore, these factors are considered to be among those that are TACE-unsuitable. It is important to identify TACE-unsuitable cases even during the course of TACE treatment and to identify Len-suitable cases while maintaining hepatic reserve.

IMPACT OF LENVATINIB ON PRESERVING LIVER FUNCTION

A sub-analysis of the REFLECT trial examined the time to progression of Child-Pugh score 6 before lenvatinib treatment to a Child-Pugh score of 7. The median time to progression to Child-Pugh score 7 was 23.7 mo in the sorafenib group, 23.9 mo in the lenvatinib 8 mg group, and 15.9 mo in the lenvatinib 12 mg group, respectively. There was no significant difference between the sorafenib and lenvatinib groups. Both sorafenib and lenvatinib affected liver functional reserve, but the difference was not significant [35].

Terashima *et al* [55] reported that patients treated with lenvatinib had a Child-Pugh score that was maintained or improved after 4 and 12 wk compared with those treated with sorafenib ($P = 0.048$ and $P = 0.036$, respectively) in clinical settings. Lenvatinib was identified as one of the factors associated with maintaining Child-Pugh scores. On multivariate analysis, a worse Child-Pugh score after 4 wk was an independent predictor of poor OS. Patients treated with lenvatinib for advanced HCC maintained their liver functional reserves better than those treated with sorafenib.

Uchikawa *et al* [56] assessed the ALBI score as an index of liver function during sorafenib and lenvatinib treatment. The median ALBI score was -2.53 before MTA treatment and -2.45, -2.44, and -2.36 post-2, -4, and -6 mo, respectively. The ALBI

scores tended to increase during MTA treatment. When examined separately in the sorafenib and lenvatinib groups, no significant difference was observed between the two groups. However, the ALBI scores of the sorafenib group increased 2 mo after treatment initiation, and at 4 and 6 mo, significant differences were observed ($P < 0.01$). Based on the above, although the ALBI score may gradually decrease with the course of MTA treatment, lenvatinib may have a lower effect on the deterioration of the ALBI score than sorafenib.

Hiraoka *et al*[57] compared the ALBI score at the start of lenvatinib with scores after 2 and 4 wk; decreased liver function was common in the early stages after starting lenvatinib (within 4 wk, especially within 2 wk). It is important to introduce MTA to patients with as good liver function as possible, taking into account the early decrease in liver function due to lenvatinib. These results suggest that ALBI grade 1 and lenvatinib at the start of MTA treatment may be related to the maintenance of liver functional reserve.

TREATMENT OUTCOME FOR THOSE WHO DO NOT MEET THE REFLECT TRIAL ELIGIBILITY CRITERIA

In the REFLECT trial, patients were excluded if they had a treatment history of MTA, large HCC with more than 50% liver occupation, HCC with main portal vein invasion, Child-Pugh grade B, platelet count $< 75 \times 10^9/L$, or apparent bile duct invasion.

We reported the efficacy and safety of lenvatinib in patients with unresectable HCC who did not meet the REFLECT eligibility criteria in clinical settings[58,59]. The ORR and the median PFS was similar between patients who met the REFLECT inclusion criteria and those who did not. Thus, the study results support the use of lenvatinib for patients with unresectable HCC who do not meet the REFLECT inclusion criteria.

But, the efficacy and tolerability of lenvatinib treatment differed according to the eligibility criteria of the REFLECT trial.

Chuma *et al*[60] reported that lenvatinib treatment offers benefits in highly advanced HCC (tumors with more than 50% liver occupation or main portal vein invasion) patients with good liver function or nodular-type tumors. Maruta *et al*[61] also reported that lenvatinib had potential profits for patients with advanced HCC with second- or later-line therapies and a high burden of intrahepatic lesions. The various characteristics identified in these studies may be useful as indicators for lenvatinib treatment in highly advanced HCC cases, which are considered treatment-resistant cancers.

POST-PD TREATMENT AFTER LENVATINIB

In the REFLECT trial, among the 954 patients randomized to receive first-line lenvatinib ($n = 478$) or sorafenib ($n = 476$), 340 patients received subsequent anticancer medication during the survival follow-up period: 156 patients (32.6%) had received first-line lenvatinib, and 184 patients (38.7%) had received first-line sorafenib[62]. Of the patients who were treated with first-line lenvatinib, the most common subsequent carcinostatic substance was sorafenib (25.3%), and the most common subsequent non-anticancer medication treatment was TACE (56.6%). The OS of patients who were initially randomized to first-line lenvatinib (versus first-line sorafenib) and who received any subsequent anticancer medication was 20.8 mo *vs* 17.0 mo (HR = 0.87; 95%CI: 0.67-1.14). The OS of patients who initially received first-line lenvatinib (versus first-line sorafenib) and who did not receive any subsequent carcinostatic substance was 11.5 mo *vs* 9.1 mo (HR = 0.90, 95%CI: 0.75-1.09). In the -hoc analysis of all patients in the REFLECT study, the OS of those who received subsequent anticancer medication was prolonged compared with patients who did not receive any subsequent anticancer medication. In the REFLECT trial, the lenvatinib group had significantly longer PFS than the sorafenib group, but superiority in OS could not be demonstrated because of the effect of post-treatment on post-progression survival prolongation.

Lenvatinib is the preferred agent for TACE-unsuitable patients in the intermediate stage based on the high RR, survival benefit over TACE, and the possibility of conversion to resection or ablation therapy[49]. Sorafenib combined with surgical resection is a feasible option in advanced HCC patients; if sorafenib is effective, long-term survival may be achieved[63]. Additional surgery was the most significant factor

predicting survival exceeding 3 years ($P < 0.0001$) and represents an independent prognostic factor (HR = 0.07, 95%CI: 0.003-0.40, $P = 0.01$)[64]. Long-term survival may be obtained for select patients with HCC receiving adequate additional surgical treatment, even after sorafenib induction. Therefore, lenvatinib treatment, which has a higher RR than sorafenib, is expected to increase the number of cases that can be switched to conversion therapy.

CONCLUSION

Many MTAs and immunotherapies have become available as treatment options for advanced HCC. Lenvatinib has been shown to have a good therapeutic effect, even in TACE-refractory and TACE-unsuitable cases. Intermediate-stage HCC beyond the up-to-seven criteria with Child-Pugh grade A/ALBI grade 1 usually does not benefit from TACE, whereas lenvatinib provides a better outcome than TACE.

Lenvatinib also has good therapeutic performance even in cases of non-simple nodular, poorly differentiated, tumor masses with more than 50% involvement of the liver and main portal vein invasion, which are generally recognized as having a poor prognosis with existing treatments. To maximize the therapeutic effect of lenvatinib in such cases, it is necessary to preserve liver function in patients with Child-Pugh grade A and ALBI grade 1 at the start of treatment.

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