Review Article | Intervention

eISSN 2005-8330
https://doi.org/10.3348/kjr.2021.0229
Korean J Radiol 2021;22(11):1822-1833

Korean Journal of Radiology
KJR

Emerging Trends in the Treatment of Advanced Hepatocellular Carcinoma: A Radiological Perspective

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This is a narrative review of various treatment modalities for advanced hepatocellular carcinoma (HCC), with a focus on recent updates in radiological treatments, as well as novel treatment concepts related to immune checkpoint inhibitors and combination therapies with locoregional treatments. Interventional radiologists have made efforts toward developing alternative and/or combination treatments for first-line systemic treatment of patients with advanced HCC. Locoregional treatments with or without systemic therapy may be considered in the selected patients. Various treatment modalities for advanced HCC are emerging, and several randomized controlled trials, including those of combination treatments with immunotherapy, are ongoing.

Keywords: *Hepatocellular carcinoma; Locoregional therapy; Transarterial chemoembolization; Transarterial radioembolization; Immunotherapy; Combined modality therapy*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and the most common malignancy among primary liver cancers [1]. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, advanced HCC (BCLC stage C) is defined as HCC in patients with a performance status of 1–2, Child-Pugh score A or B, macrovascular invasion (MVI), and/or extrahepatic spread (EHS) (Fig. 1) [2]. Unfortunately, almost 40% of patients have advanced stages at the time of the first diagnosis, and their prognoses are dismal [3].

Sorafenib is currently the treatment of choice for patients with advanced HCC. However, its efficacy is suboptimal; it is associated with a median overall survival (OS) extension of 2–3 months [4,5]. In addition, almost 35% of patients require dose reduction and another 15% are intolerant to sorafenib and require its withdrawal. Thus, sorafenib therapy is suitable for only half of the patients with advanced HCC [6]. Lenvatinib, compared with sorafenib, was associated with non-inferior OS as first-line therapy for patients with unresectable HCC [7]. Recently, a phase-3 trial (IMbrave150) showed that the combination of atezolizumab and bevacizumab had superior OS and progression-free survival (PFS), with sorafenib as the first-line treatment for unresectable HCC (including 81% BCLC C patients) [8].

For patients with advanced HCC, several institutions have administered other locoregional therapies or combination treatments performed by interventional radiologists instead of sorafenib monotherapy. Other emerging alternative and/or combination treatments, including immune checkpoint inhibitors, have also recently been investigated for their ability to improve the OS of patients with advanced HCC. In this descriptive paper, these various treatment modalities are comprehensively reviewed, with a focus on recent updates to radiologic treatments (Table 1).

Transcatheter Arterial Chemoembolization

Transcatheter arterial chemoembolization (TACE) is

Received: March 11, 2021 **Revised:** May 17, 2021
Accepted: June 3, 2021
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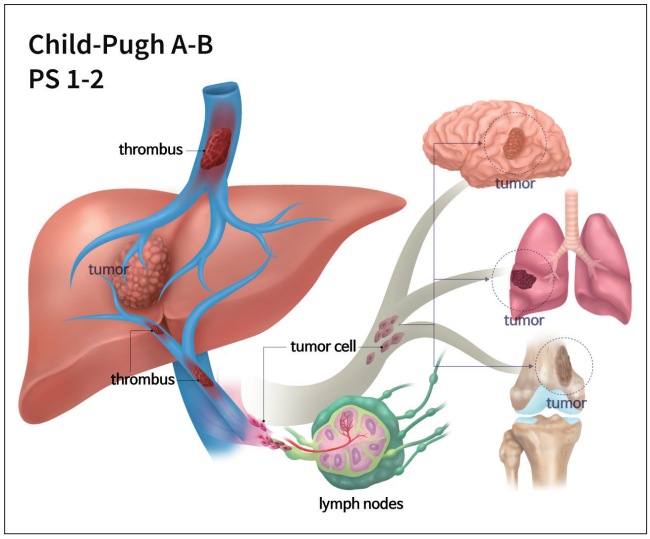

Fig. 1. Schematic image of advanced HCC (BCLC stage C).
Advanced HCC (BCLC stage C) is defined as HCC in patients with performance status 1–2, Child-Pugh score A or B, macrovascular invasion, and/or extrahepatic spread. BCLC = Barcelona Clinic Liver Cancer, HCC = hepatocellular carcinoma

a well-established treatment for non-resectable HCC and is used as the first-line therapy in almost half of the patients with advanced HCC [9]. Although TACE is hypothetically contraindicated in HCC with portal vein (PV) tumor thrombosis (PVTT) because of the potential risk of hepatic ischemia, several studies have verified that TACE can be safely performed in the presence of adequate collateral circulation around the involved PV [10,11]. As an alternative to conventional TACE, non-resorbable microspheres loaded with a chemotherapeutic agent, known as drug-eluting beads (DEBs), can be administered to ensure sustained and selective drug delivery to the tumor with increased local drug concentration without elevation of systemic concentration [12].

Randomized Controlled Trial(s)

TACE improved the survival of selected patients with unresectable HCC (including 12.5% BCLC C patients) [13]. There have been no randomized controlled trials (RCTs) comparing TACE and sorafenib in patients with advanced HCC.

Observational Studies

Pinter et al. [14] reported that TACE and sorafenib were associated with similar OS (9.2 vs. 7.4 months, respectively, $p = 0.377$) in patients with advanced HCC. However, candidates for TACE should still be carefully selected when PVTT is present. In a study of 331 HCC patients with

Table 1. Summary of Radiologic Treatment Options for Advanced Hepatocellular Carcinoma

Treatment	Number of Studies [References]	Median OS (Months)	Median PFS (Months)	Extent of MVI (mOS, Months)			EHS (mOS, Months)	Grade 3/4 AE (%)
				Main PV	Branch PV	HV/IVC		
Single therapy								
Conventional TACE	8 [11,14,15,25-29]	6–14.9		3–7.1	10.2		4.0–9.0	5.4–38
DEB-TACE	3 [16-18]	13.3–19.5	5.1		20			13.3
RE	12 [33-36,38-44,46]	6–45.3	3.4–6.5	4.4–9.7	9.9–16.9		5.4–7.4	9–48
Sorafenib combination therapy								
TACE + sorafenib	7 [52-58]	7.0–16.2	4.8–12.6	3–7.8	13–15		8–16	12.2–35
RFA (with TACE) + sorafenib	2 [61,62]	14.0–19.0		11.0–19.0	16.0			
RE + sorafenib	5 [65-69]	8.6–18.5	6.5–12.3					21.1–64.8
Radiation combination therapy								
TACE + RT	7 [72-78]	5.9–24.2	6.5–10.0	12		11.7	6	9.4–19.9
ICI combination therapy								
TACE/RFA + ICI	1 [85]	12.3						53.1
RE + ICI	2 [86,88]	15.1–16.5	4.6–5.7					11–19.2

AE = adverse event, DEB = drug eluting bead, EHS = extrahepatic spread, HAIC = hepatic arterial infusion chemotherapy, HV = hepatic vein, ICI = immune checkpoint inhibitor, IVC = inferior vena cava, mOS = median OS, MVI = major vascular invasion, OS = overall survival, PFS = progression-free survival, PV = portal vein, RE = radioembolization, RFA = radiofrequency ablation, RT = radiotherapy, TACE = transcatheter arterial chemoembolization

https://doi.org/10.3348/kjr.2021.0229

segmental PVTT [15], four risk factors were associated with poor patient survival: a major tumor burden, EHS, non-regression following TACE (stable or progressive disease), and a Child-Pugh score of B. The expected median OS of HCC patients with 0, 1, or 2–4 risk factors were 29.1, 15.1, and 5.3 months, respectively. TACE may not be recommended for patients with 2–4 risk factors, owing to poor survival outcomes.

In patients with advanced HCC, the median OS associated with the use of DEB-TACE ranged from 13.3 to 19.5 months [16-18]. However, the comparative efficacy and survival rates of DEB-TACE and conventional TACE have not been established. Several studies have reported no significant difference between the survival outcomes associated with DEB-TACE and conventional TACE [19-22]. However, a study by Li et al. [23] demonstrated more favorable PFS and OS in the DEB-TACE group and reported that DEB-TACE was an independent predictive factor for a better objective response rate, PFS, and OS. Recently, Chu et al. [24] reported a significantly higher objective tumor regression rate in a DEB-TACE group in a subgroup analysis of BCLC C patients (17.7% vs. 10.3%, $p = 0.033$), although the subgroup analysis showed no significant difference in the time to progression (TTP). In addition, lesser post-procedural abdominal pain [19], fewer required treatments [20], better tolerability [21], and shorter hospital stays [22] have been widely reported in DEB-TACE groups. The current findings do not provide any evidence demonstrating the superiority of DEB-TACE or conventional TACE based on survival outcomes, although DEB-TACE may be more suitable for vulnerable patients or those anticipated to show deterioration following locoregional chemotherapy.

Jung et al. [25] found that intrahepatic tumor status was a significant predictor of survival in patients with advanced HCC, even in the case of metastasis. Several studies, including those on metastatic HCC, reported that treatment with intrahepatic TACE, compared with no therapy, was associated with improved survival [26,27]. Kirstein et al. [28] showed the non-inferiority of TACE to sorafenib based on the median OS in patients with limited EHS after propensity score matching (8 vs. 4 months, $p = 0.613$); however, in selected patients with low alpha fetoprotein and C-reactive protein concentrations, TACE showed a prolonged median OS of 20 months. In addition, Kim et al. [29] reported no significant difference in OS between the TACE and sorafenib subgroups of the HCC patients with EHS ($p = 0.063$). In the subgroup analysis, TACE was associated with better survival among younger patients and those with segmental/lobar PV invasion.

Summary

TACE for patients with advanced HCC has shown benefits in some observational studies and may be considered in selected patients who are not suitable for sorafenib, albeit the low level of evidence [6,30].

Radioembolization

Transarterial radioembolization with yttrium-90 (^{90}Y) in resin or glass microspheres has been conducted as an alternative to TACE [31]. Radioembolization differs from TACE in that it uses a local beta radiation mechanism instead of arterial occlusion. Pretreatment technetium-99m macroaggregated albumin scan and angiography are essential for assessing lung shunt fraction and identifying vessels that may supply the gastrointestinal (GI) tract to avoid radiation pneumonitis (< 1%) and GI ulceration (< 5%). Radioembolization causes less post-embolization syndrome than TACE because the embolic effect is minimal. Other complications, including radiation-induced liver disease, radiation cholecystitis, biloma, liver abscess, and bile duct stricture, are infrequent [32].

Randomized Controlled Trial(s)

Milestone trials have compared radioembolization and sorafenib in locally advanced HCC [33-35]. The SIRveNIB trial [33] demonstrated no statistically significant difference in the median OS (8.8 vs. 10.0 months, $p = 0.36$), and the SARAH trial [34] showed comparable median OS (8.0 vs. 9.9 months, $p = 0.18$) or PFS. However, radioembolization was associated with significantly fewer grade 3 or 4 adverse events (AEs) in both the SIRveNIB and SARAH studies. However, the DOSISPHERE-01 trial [36] compared the personalized boosted dosimetry (≥ 205 Gy) and the standard dosimetry (120 ± 20 Gy) subgroups of locally advanced HCC patients and showed better median OS (26.6 vs. 10.7 months, $p = 0.010$) and higher objective response rate (71% vs. 36%, $p = 0.007$) in the former than in the latter group. This study may challenge the conclusions of previous RCTs of radioembolization, in which no personalized dosimetry was used.

Meta-Analysis

Patients with HCC with PVTT have shown poor response

https://doi.org/10.3348/kjr.2021.0229

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rates to sorafenib (only 2–3.3%) in two randomized trials [4,5], and several physicians prefer radioembolization treatment for HCC invading the PV. A meta-analysis of observational studies [37] revealed that radioembolization was associated with a higher pooled OS at 6 months/1 per year (76% vs. 54%/47% vs. 24%) and a longer TTP than sorafenib in the treatment of HCC with PVTT. In addition, radioembolization was associated with a lower incidence of AEs of grades higher than 3 (9% vs. 28%).

Observational Studies

Two cohort studies [38,39] demonstrated a median OS of 10–12 months for advanced HCC. A prospective phase II study reported a median OS of 13 months in patients with locally advanced HCC with PVTT [40]. The presence and extent of PVTT affect prognosis, with reported median OS durations of 9.9–16.6 months for branch PVTT and 4.4–9.7 months for main PVTT when a distinction of the PVTT extent was made [38,39,41-43]. Zu et al. [44] reported that the median OS of advanced HCC patients with Child-Pugh B7–9 (5.5–6.0 months) was significantly worse than those with Child-Pugh A (20.2 months).

Ablative radioembolization is intended to deliver high-dose radiation (with a target dose of greater than 190 Gy) to the liver segment or lobe where the cancer is located, inducing a maximum cytotoxic effect within the targeted area with the delivery of radioactivity to kill the tumors and adjacent normal liver parenchyma [45]. A recent study by Cardarelli-Leite et al. [46] demonstrated that ablative radioembolization was associated with a longer survival duration than conventional radioembolization in patients with advanced HCC and PVTT without EHS; ablative radioembolization was associated with a longer median OS (45.3 vs. 18.2 months, $p = 0.003$) and improved 4-year survival (53.9% vs. 11.2%). Neither modality was associated with toxic effects on liver function. In addition, the LEGACY study investigating high-dose radioembolization [47] showed a high objective response rate (88.3%) and better 3-year OS rate (86.6%) in patients with unresectable solitary HCC without MVI or EHS (including 39.5% BCLC C patients).

Summary

Two RCTs demonstrated that there was no significant difference in the OS after radioembolization and sorafenib treatment. Patients with locally advanced HCC and preserved liver function who have contraindications for sorafenib may be good candidates for radioembolization [6,30]. The promising results of the administration of radioembolization with boosted dose warrant further RCTs either alone or in combination with other agents [36,48].

Combined TACE and Sorafenib

The efficacy of TACE in combination with sorafenib has been investigated, as these two treatment options are anticipated to work synergistically. TACE-induced acute hypoxia in surviving tumor cells leads to the upregulation of angiogenic growth factors, which may contribute to revascularization of the tumor, local recurrence, or metastasis [49,50]. Sorafenib inhibits tumor cell proliferation by exerting antiangiogenic effects by blocking vascular endothelial growth factor (VEGF) receptor-2 and -3, and platelet-derived growth factor (PDGF) receptor tyrosine kinase [51]. However, studies on the comparative efficacy and survival rates of TACE plus sorafenib and sorafenib alone have reported conflicting results, whereas the survival benefit of combination treatment has been observed in certain subgroups.

Randomized Controlled Trial(s)

A phase III STAH trial [52] demonstrated that the combination of sorafenib and TACE (n = 170), compared with sorafenib alone (n = 169), did not improve OS in patients with advanced HCC (12.8 vs. 10.8 months, $p = 0.290$), although combination therapy did show significantly improved TTP (5.3 vs. 3.5 months, $p = 0.003$), PFS (5.2 vs. 3.6 months, $p = 0.009$), and tumor response rate (60.6% vs. 47.3%, $p = 0.005$). A post-hoc subgroup analysis revealed that the OS in the combination group receiving two or more concurrent TACE procedures was longer than that in the sorafenib alone group (18.6 vs. 10.8 months, $p = 0.006$). Grade 3 or 4 AEs occurred more frequently in the combination group than in the sorafenib alone group (33.3% vs. 19.8%, $p = 0.006$).

Observational Studies

Choi et al. [53] reported that the median OS and TTP of the TACE plus sorafenib group, compared with those of the sorafenib-only group of advanced HCC patients, improved; however, after propensity score matching (96 pairs), the improvement reduced and only TTP remained significant. In another retrospective study of advanced HCC patients with main PVTT [54], TACE plus sorafenib, compared to sorafenib,

 https://doi.org/10.3348/kjr.2021.0229

offered no significant benefit related to OS (7.0 vs. 6.0 months, $p = 0.544$) or TTP (3.0 vs. 3.0 months, $p = 0.924$). Ha et al. [55] compared the efficacies of TACE combined with sorafenib and sorafenib alone for advanced HCC. In their study, the patients were divided into three different groups (concurrent TACE with sorafenib, TACE followed by sorafenib, and sorafenib alone), and their median OS were comparable (16.2, 13.5, and 11.8 months, respectively, $p = 0.13$). However, among PV invasion cases, TACE administered concurrently with or before sorafenib treatment was associated with improved survival (25.7 months, $p = 0.002$; 14.0 months, $p = 0.030$, respectively) compared with sorafenib monotherapy (5.5 months). Multivariate analysis showed that sorafenib duration, TACE, and Child-Pugh scores were associated with a survival benefit. Chien et al. [56] showed that combining TACE with sorafenib resulted in better OS than sorafenib alone in advanced HCC patients with a Child-Pugh score A after propensity score matching (419 vs. 223 days, $p = 0.028$). Hsiao et al. [57] demonstrated that the concurrent administration of TACE and sorafenib resulted in significantly higher median OS in advanced HCC patients than sorafenib alone (14.2 vs. 7.5 months, $p = 0.048$).

According to the GIDEON study [58], there is a global variation in the combination of TACE with sorafenib in HCC patients; 1511 (47.2%) patients underwent sorafenib after TACE, and 325 (10.1%) underwent TACE concomitantly. The data revealed concomitant TACE to show a significant benefit in median OS in advanced HCC patients in comparison with non-concomitant TACE (15.5 vs. 8.3 months). However, this study was affected by significant heterogeneity in tumor invasiveness, metastasis patterns, and liver function across the groups.

Summary

One RCT showed that sorafenib combined with TACE did not improve OS. However, combination treatment significantly improved tumor response and secondary outcomes. The survival benefit of this combination treatment has been observed in certain subgroups in several observational studies.

Combined Radiofrequency Ablation (with TACE) and Sorafenib

Given that the cause of death in most patients with advanced HCC is intrahepatic tumor progression rather than EHS [59], debulking of the primary tumor burden is considered to show survival benefits in patients with advanced HCC [60].

Randomized Controlled Trial(s)

A western RCT in HCC patients with main PVTT and no EHS by Giorgio et al. [61] demonstrated that sorafenib combined with radiofrequency ablation (RFA) of both intraparenchymal HCC and the main PVTT showed better OS than sorafenib alone (1-, 2-, and 3-year survival rates of 60% vs. 37%, 35% vs. 0%, and 26% vs. 0%, respectively; hazard ratio [HR]: 2.87, $p < 0.001$). Multivariate analysis showed that the combined use of RFA and sorafenib was the only independent predictor of survival (HR: 2.89, $p < 0.001$).

Observational Studies

A multicenter retrospective study [62] showed that TACE-RFA combined with sorafenib was safe and effective in patients with advanced recurrent HCC after initial liver resection with PVTT involving the right or left PV or higher or EHS. This combination treatment was found to be superior to sorafenib based on the median OS (14.0 vs. 9.0 months, $p < 0.001$) and TTP (7.0 vs. 4.0 months, $p < 0.001$). Multivariate analysis showed that the treatment modality was a significant predictor of OS and TTP, and the number of intrahepatic tumors was also a prognostic factor for OS.

Summary

RFA combined with sorafenib showed better OS than sorafenib alone in patients with advanced HCC; thus, this combination may be an alternative treatment option.

Combined Radioembolization and Sorafenib

The theory behind the combined use of radioembolization and sorafenib is based on the mechanism by which sorafenib enhances the radiosensitivity of human HCC cell lines through the selective inhibition of the radiation-induced activation of vascular endothelial growth factor receptor 2 (VEGFR2) and extracellular-signal-regulated kinase pathways, thus promoting radiation-induced apoptosis [63]. However, Lewandowski et al. [64] reported that the predominant effect of adding sorafenib may be through the inhibition of PDGF and not VEGF.

Randomized Controlled Trial(s)

A SORAMIC study [65] comparing the efficacy and safety

https://doi.org/10.3348/kjr.2021.0229

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of radioembolization plus sorafenib with sorafenib alone in patients with advanced HCC found that the addition of radioembolization to sorafenib did not demonstrate significantly better OS than sorafenib alone (12.1 vs. 11.4 months, $p = 0.953$). However, subgroup analyses led to hypothesis-generating results related to patients with potential clinical benefits from adding radioembolization to sorafenib, with such patients possibly including non-cirrhotic HCC patients (HR: 0.46, $p = 0.013$), those with cirrhosis with a non-alcoholic etiology (HR: 0.63, $p = 0.009$), and patients aged ≤ 65 (HR: 0.65, $p = 0.046$). The STOP-HCC study (NCT01556490) comparing radioembolization plus sorafenib with sorafenib alone is also currently underway and the results will be available soon.

Observational Studies

Kaseb et al. [66] conducted a phase 2 study of advanced HCC patients (including patients with metastasis) that showed that the combination of radioembolization and sorafenib was tolerable, and it was associated with improved OS and PFS (18.5 and 12.3 months) compared with previous reports evaluating sorafenib alone. The combination of radioembolization and sorafenib for advanced HCC patients is reported to be well-tolerated, with the median OS durations reported by several investigations [67-69] ranging from 8.6–12.4 months, which are longer than those reported for sorafenib alone in similarly designed reports.

Summary

The combined use of radioembolization and sorafenib, compared with sorafenib alone, did not result in a significant improvement in OS. However, this combination treatment may be an option for selected patients with advanced HCC.

Combined TACE and Radiotherapy

The efficacy of TACE combined with radiotherapy (RT) has been investigated, as it is expected to result in better outcomes in advanced HCC patients. The rationale for this combination therapy is that reducing PVTT with RT can inhibit tumor growth in blood vessels and preserve proper portal venous blood flow to prevent the deterioration of liver function, limit intrahepatic tumor spread, and promote subsequent treatments of primary tumors [70]. In addition, RT may potentially boost the effects of TACE by causing regression of the arteriovenous shunt around the PVTT [71].

Randomized Controlled Trial(s)

Yoon et al. [72] conducted an RCT comparing the efficacies of TACE plus RT (n = 45) and sorafenib (n = 45) in 90 patients with locally advanced HCC with MVI. At 12 weeks, the PFS rate was significantly higher in the TACE plus RT group than in the sorafenib group (86.7% vs. 34.3%, $p < 0.001$). The TACE plus RT group demonstrated a significantly higher radiologic response rate at week 24 (15 [33.3%] vs. 1 [2.2%], $p < 0.001$) and significantly improved median TTP (31.0 vs. 11.7 weeks, $p < 0.001$), PFS (30.0 vs. 11.3 weeks, $p < 0.001$), and OS (55.0 vs. 43.0 weeks, $p = 0.04$) compared with the sorafenib group. The AEs of grades 3–4 in the two groups were similar ($p = 0.18$), and no patients in the TACE plus RT group discontinued treatment because of hepatic decompensation.

Observational Studies

Chung et al. [73] reported a median OS of 12 months in patients with HCC with the main PVTT treated with TACE plus RT. Kim et al. [74] evaluated the efficacy of TACE plus RT as a first-line treatment in 639 patients with HCC and MVI. The median OS was 10.7 months, with 1- and 2-year survival rates of 46.5% and 23.9%, respectively. For HCC with inferior vena cava tumor thrombosis, a prospective study [75] evaluated the effects of TACE plus RT and TACE alone in a historical control group. The results showed that the median OS was significantly higher in the TACE plus RT group than in the TACE group (11.7 vs. 4.7 months, $p < 0.01$).

Kim et al. [76] compared the efficacy of TACE with or without RT with that of sorafenib alone for advanced HCC with PVTT. In the propensity score-matched analysis, the TACE plus RT group demonstrated longer OS and TTP than the group that received TACE alone (102 pairs; 11.4 vs. 7.4 months, $p = 0.023$; 8.7 vs. 3.6 months, $p < 0.001$, respectively) or sorafenib alone (30 pairs; 8.2 vs. 3.2 months, $p < 0.001$; 5.1 vs. 1.6 months, $p < 0.001$, respectively). Shen et al. [77] evaluated the survival outcomes of TACE plus RT and TACE plus sorafenib in advanced HCC patients with MVI. After propensity score matching, TACE plus RT provided improved OS (24.2 vs. 8.4 months, $p = 0.007$) and PFS (10.0 vs. 3.5 months, $p < 0.001$) compared with TACE plus sorafenib. However, a recent study by Chu et al. [78] comparing TACE plus RT (n = 203) with TACE plus sorafenib (n = 104) in advanced HCC with PVTT demonstrated conflicting results. The median OS and PFS in the two groups were not significantly different after propensity score matching (n = 87). However, in a subgroup

https://doi.org/10.3348/kjr.2021.0229

analysis of non-metastatic advanced HCC patients, TACE plus RT showed better OS (HR: 1.42; 95% confidence interval [CI]: 1.00–2.03; $p = 0.05$) and PFS (HR: 1.35; 95% CI: 0.98–1.86; $p = 0.071$) than TACE plus sorafenib, with borderline statistical significance.

Summary

One RCT and several observational studies have shown that TACE plus RT could be considered a first-line treatment option for patients with locally advanced HCC [30].

Immunotherapy

Immune checkpoint inhibitors have demonstrated promising benefits for the treatment of patients who are intolerant to or have progressed under approved multikinase inhibitors in recent phase II clinical trials. In the CheckMate040 study [79], nivolumab, a programmed cell death protein 1 (PD-1) immune checkpoint inhibitor, provided a median OS of 15.0 months (95% CI: 9.6–20.2 months) in the dose-escalation phase. The KEYNOTE-224 study [80] showed a comparable result for median OS with pembrolizumab (12.9 months; 95% CI: 9.7–15.5 months).

Interventional radiological treatments including TACE, radioembolization, and ablation can increase tumor immunogenicity by stimulating a pro-immune inflammatory response and releasing tumor-associated antigens, which can lead to an increase in the systemic antitumor immune response, including tumor-infiltrating cytotoxic CD8+ T cells [81], thus providing a solid rationale for the combination treatment with immunotherapy. Furthermore, immunotherapy has an advantage in that it does not require liver metabolism [82]. In several preclinical studies, the combination of locoregional treatments with immune checkpoint inhibitors demonstrated an increased antitumor immune response [83]. Recently, Craciun et al. [84] compared intra-tumor immune infiltrates in surgical specimens after preoperative treatment with TACE or radioembolization. Significantly increased recruitment/activation of intra-tumor immune cells (tumor-infiltrating lymphocytes, and CD4+ and CD8+ T cells) was observed in the radioembolization group compared to the groups that underwent TACE or no preoperative treatment. The authors suggested that radioembolization is a better option than TACE in combination with an immune checkpoint inhibitor.

Currently, several studies investigating the efficacy of combinations of various immunotherapies with TACE, radioembolization, or ablation are underway, and the role of combination treatment using immunotherapy in advanced HCC patients should be determined in the foreseeable future.

Combined Immunotherapy and TACE or RFA

Duffy et al. [85] evaluated the efficacy of combining tremelimumab (anti-CTLA-4 monoclonal antibody) with TACE or ablation in 32 patients with advanced HCC. Most (75%) of the patients were intolerant of sorafenib or progressed on it previously, and all patients had evidence of progressive disease at enrollment. The median OS and TTP were 12.3 months (95% CI: 9.3–15.4) and 7.4 months (95% CI: 4.7–19.4), respectively. The majority of patients experienced a marked reduction in HCV load, objective tumor responses outside of the embolized or ablated zone, and infiltration of intratumoral CD8+ T cells.

To date, multiple trials of TACE plus nivolumab (NCT03143270, NCT03572582, NCT04268888), TACE plus pembrolizumab (NCT03397654, NCT03099564), and ablation plus nivolumab (NCT03383458) are recruiting patients. In addition, a trial of TACE plus durvalumab and bevacizumab (NCT03778957) is currently recruiting patients, as the literature proposes a synergistic effect for immunotherapy and anti-angiogenic therapy.

Combined Immunotherapy and Radioembolization

A retrospective study [86] including 26 patients with advanced (n = 21) or aggressive intermediate stage HCC demonstrated the efficacy of combined immune checkpoint inhibitor therapy (nivolumab and ipilimumab plus nivolumab) within 3 months of radioembolization. From the first radioembolization, the median OS and PFS were 16.5 months (95% CI: 6.6–26.4) and 5.7 months (95% CI: 4.3–7.1), respectively. Nine patients (35%) maintained disease control, and one patient had a complete response on imaging that was pathologically confirmed after liver explantation. The combination treatment resulted in limited treatment-related toxicity. In addition, a case report [87] from another institution showed that combining nivolumab with radioembolization in an advanced HCC patient with MVI successfully bridged the patient to surgery. The pathological report showed negative margins with a complete pathological response.

https://doi.org/10.3348/kjr.2021.0229

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A phase II nonrandomized trial [88] combining nivolumab and radioembolization in Asian patients with advanced HCC (n = 36) showed an encouraging overall response rate of 31%, with median PFS and OS of 4.6 months (95% CI: 2.3–8.4) and 15.1 months (95% CI: 7.8–not evaluable), respectively. Only 11% of the patients showed grade 3–4 AEs. Marinelli et al. [89] evaluated the efficacy and safety of combining nivolumab with TACE or radioembolization in 17 patients with advanced HCC. The median OS and TTP were 11.3 months and 7.9 months, respectively. No AEs of grades 3–4 attributable to immunotherapy were observed. Furthermore, trials evaluating radioembolization plus nivolumab (NCT03380130, NCT03033446, NCT02837029) and radioembolization plus pembrolizumab (NCT03099564) are currently recruiting patients.

CONCLUSION

Interventional radiologists have made efforts toward developing alternative and/or combination treatments for first-line systemic treatment for patients with advanced HCC. Locoregional treatments with or without systemic therapy may be considered in the selected patients. However, all RCTs compared locoregional therapy alone or in combination with systemic therapy to sorafenib alone, and the shift of the standard systemic therapy to atezolizumab plus bevacizumab can influence the interpretation of the results of previous studies. In addition, in the BCLC staging system, advanced HCC includes heterogeneous patient populations; therefore, subclassifications for accurate prognosis prediction are needed, which should also be appropriate for interpreting clinical trials and comparing treatment modalities. Various treatment modalities for advanced HCC continue to evolve, and several RCTs, including those of combination treatments with immunotherapy, are ongoing.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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