Liver Cancer

Liver Cancer 2020;9:367–377
DOI: 10.1159/000507934
Received: April 3, 2020
Accepted: April 16, 2020
Published online: June 29, 2020

Editorial

A Paradigm Change in the Treatment Strategy for Hepatocellular Carcinoma

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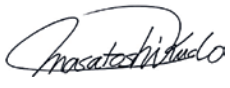

Editor *Liver Cancer*

Keywords
Hepatocellular carcinoma · Treatment strategy

Japan has the best treatment outcomes for hepatocellular carcinoma (HCC) worldwide [1, 2]. The 20th Nationwide Follow-Up Survey of Primary Liver Cancer in Japan reported a median survival time of 61 months, a 5-year survival rate of 50.4%, and a 10-year survival rate of 24% among 65,711 patients with HCC whose data were compiled from approximately 600 institutions across Japan between 2002 and 2009 [3]. The survey included patients of all stages, ranging from single very-early-stage HCC of 2 cm or smaller, to advanced-stage HCC with vascular invasion or extrahepatic spread, to terminal-stage Child-Pugh C HCC. Establishment of a nationwide surveillance system of patients at a high risk of progressing from hepatitis C- or B-related cirrhosis to HCC in Japan has enabled HCC to be detected at an early stage (≤3 tumors of ≤3 cm each, or a single tumor ≤5 cm) in more than 60% of patients, most of whom undergo potentially curative treatment such as resection or ablation. About 30% of patients whose HCC is detected at an intermediate stage undergo transarterial chemoembolization (TACE). The remaining 10% of patients have advanced HCC with vascular invasion or extrahepatic spread or terminal-stage disease with Child-Pugh C liver function at the time of diagnosis.

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Advanced HCC with vascular invasion has been actively treated with hepatic arterial infusion chemotherapy in Japan [4]. Now that Japan's surveillance system is so well established, there is a sense that the best possible treatment outcomes of resection, local ablation therapy, and TACE have been achieved. Therefore, a recent trend is that systemic therapy including combination immunotherapy being introduced into the treatment for intermediate and advanced stage HCC is going to bring the new era in the treatment of HCC.

Molecular Targeted Agents

Sorafenib, the first molecular targeted drug to show a survival benefit in patients with advanced HCC, was approved worldwide in 2007 based on the results of the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial [5] and the Asia-Pacific trial [6]. Since then, several phase III trials of molecular targeted drugs have been conducted; however, the 10-year period from 2007 to 2016 was a difficult time for the development of new HCC drugs because all the clinical trials (8 of first-line therapies and 5 of second-line therapies) conducted during that period failed (Table 1) [4–28]. This was followed by successful trials of regorafenib as a second-line therapy in 2017 [23], lenvatinib as a first-line therapy in 2018 [14], and ramucirumab [27] and cabozantinib [26] as second-line therapies in 2019. The approval of these targeted drugs resulted in a total of 5 new drug options (2 first-line and 3 second-line agents). In addition, recently the phase III IMbrave trial (atezolizumab plus bevacizumab combination therapy) has shown positive results [17]. These developments are greatly shifting the paradigm of HCC treatment.

Paradigm Change in Intermediate-Stage HCC

The biggest changes are occurring in the management of intermediate- and advanced-stage HCC. Intermediate-stage HCC is generally defined as multifocal HCC (≥4 tumors) or large HCC (tumor >5 cm). TACE was previously the only standard treatment option for this stage of disease; however, the 2017 version of the Clinical Practice Guidelines for Hepatocellular Carcinoma published by the Japan Society of Hepatology (JSH) [29] included not only TACE but also resection, hepatic arterial infusion chemotherapy, and molecular targeted therapy as recommended options for multifocal HCC and/or large HCC. Most notably, the concept of TACE-refractory HCC, first proposed by the JSH in 2010 [30] and later updated [31], was an important milestone. Subsequently, the concept of TACE-refractory HCC was adopted worldwide [32–35]. Sorafenib was not originally indicated for intermediate-stage HCC in some Asian countries; however, even those countries' health insurance systems were changed when the concept of TACE-refractory HCC was described in the Japanese Consensus-Based Clinical Practice Guidelines for Hepatocellular Carcinoma [30, 31]. In addition, 2 retrospective clinical studies showed that switching to molecular targeted therapy from TACE in refractory patients extended survival compared with repeating TACE [36, 37]. The OPTIMIS trial [38, 39], a noninterventional prospective global study conducted to validate the results of the retrospective studies, also showed that survival was extended by switching to a molecular targeted therapy after a patient had become refractory to TACE [38, 39]. It is now nearly the global consensus that TACE-refractory patients should be promptly switched to molecular targeted therapy.

Another important option in intermediate-stage HCC is a combination strategy of TACE with molecular targeted agents. After 5 negative trials [40–44], the TACTICS trial clearly showed that TACE combined with sorafenib improved progression-free survival, which was specifically defined based on the concept of unTACEable progression [45, 46].

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Table 1. Phase III clinical trials in advanced-stage HCC

Target population	Design	Trial name	Result	Presentation	Publication	First author
Advanced						
First line	1. Sorafenib vs. placebo	SHARP	Positive	ASCO 2007	NEJM 2008	Llovet [5]
	2. Sorafenib vs. placebo	Asia-Pacific	Positive	ASCO 2008	Lancet-O 2009	Cheng [6]
	3. Sorafenib vs. sunitinib	SUN1170	Negative	ASCO 2011	JCO 2013	Cheng [7]
	4. Sorafenib ± erlotinib	SEARCH	Negative	ESMO 2012	JCO 2015	Zhu [8]
	5. Sorafenib vs. brivanib	BRISK-FL	Negative	AASLD 2012	JCO 2013	Johnson [9]
	6. Sorafenib vs. linifanib	LiGHT	Negative	ASCO-GI 2013	JCO 2015	Cainap [10]
	7. Sorafenib ± doxorubicin	CALGB 80802	Negative	ASCO-GI 2016	JAMA Oncol 2019	Abou-Alfa [11]
	8. Sorafenib ± HAIC	SILIUS	Negative	EASL 2016	Lancet GH 2018	Kudo [4]
	9. Sorafenib ± Y90	SARAH	Negative	EASL 2017	Lancet-O 2017	Vilgrain [12]
	10. Sorafenib ± Y90	SIRveNIB	Negative	ASCO 2017	JCO 2018	Chow [13]
	11. Sorafenib vs. lenvatinib	REFLECT	Positive	ASCO 2017	Lancet 2018	Kudo [14]
	12. Sorafenib vs. nivolumab	CheckMate-459	Negative	ESMO 2019	Ann Oncol 2019	Yau [15]
	13. Sorafenib ± Y90	SORAMIC	Negative	EASL 2018	J Hepatol 2019	Ricke [16]
	14. Sorafenib vs. atezolizumab + bevacizumab	IMbrave150	Positive	ESMO-Asia 2019	NEJM 2020	Finn [17]
	15. Sorafenib vs. durvalumab + tremelimumab vs. durvalumab	HIMALAYA	Ongoing			
	16. Sorafenib vs. tislelizumab	Rationale301	Ongoing			
	17. Lenvatinib ± pembrolizumab	LEAP002	Ongoing			
	18. Lenvatinib or sorafenib vs. nivolumab + ipilimumab	CheckMate 9DW	Ongoing			
	19. Sorafenib vs. atezolizumab + cabozantinib	COSMIC-312	Ongoing			
Second line	1. Brivanib vs. placebo	BRISK-PS	Negative	EASL 2012	JCO 2013	Llovet [18]
	2. Everolimus vs. placebo	EVOLVE-1	Negative	ASCO-GI 2014	JAMA 2014	Zhu [19]
	3. Ramucirumab vs. placebo	REACH	Negative	ESMO 2014	Lancet-O 2015	Zhu [20]
	4. S-1 vs. placebo	S-CUBE	Negative	ASCO 2015	Lancet GH 2017	Kudo [21]
	5. ADI-PEG 20 vs. placebo	n.a.	Negative	ASCO 2016	Ann Oncol 2018	Abou-Alfa [22]
	6. Regorafenib vs. placebo	RESORCE	Positive	WCGC 2016	Lancet 2017	Bruix [23]
	7. Tivantinib vs. placebo	METIV-HCC	Negative	ASCO 2017	Lancet-O 2018	Rimassa [24]
	8. Tivantinib vs. placebo	JET-HCC	Negative	ESMO 2017	n.a.	n.a.
	9. DT vs. placebo	ReLive	Negative	ILCA 2017	Lancet GH 2019	Merle [25]
	10. Cabozantinib vs. placebo	CELESTIAL	Positive	ASCO-GI 2018	NEJM 2018	Abou-Alfa [26]
	11. Ramucirumab vs. placebo	REACH-2	Positive	ASCO 2018	Lancet-O 2019	Zhu [27]
	12. Pembrolizumab vs. placebo	KEYNOTE-240	Negative	ASCO 2019	JCO 2020	Finn [28]

HAIC, hepatic arterial infusion chemotherapy; Y90, yttrium-90 radioembolization; S-1, fluoropyrimidine comprised of tegafur, gimeracil and oteracil; ADI-PEG 20, arginine depletion with pegylated arginine deiminase; DT, doxorubicin-loaded nanoparticles; n.a., not applicable. Red, positive trials; blue, ongoing trials; black, negative trials.

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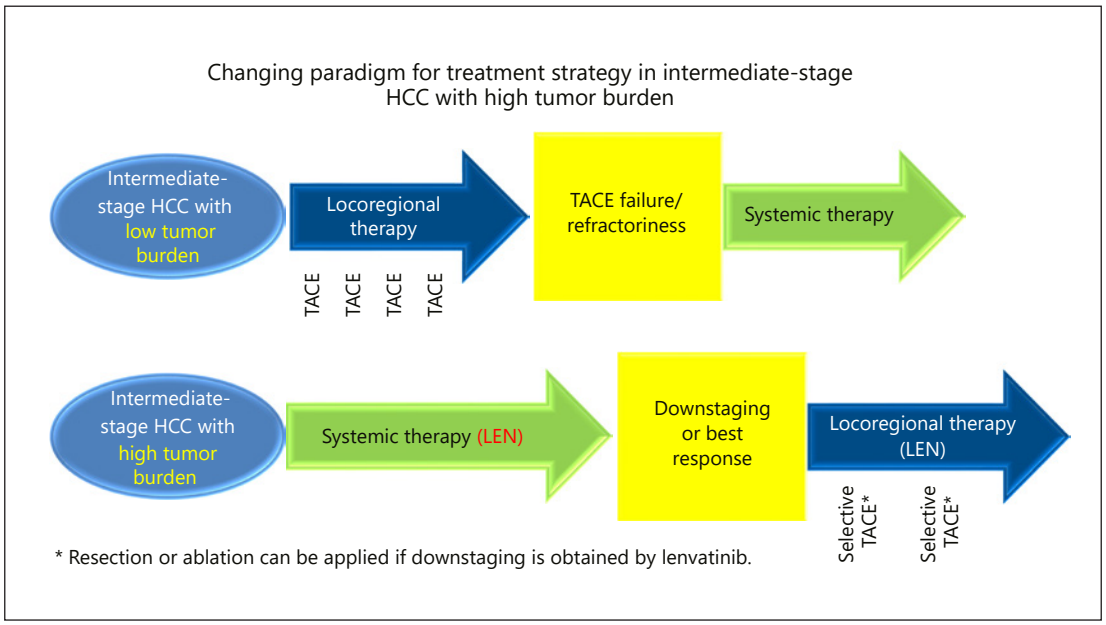

Fig. 1. Changing paradigm for treatment strategy in intermediate-stage HCC with high tumor burden. Until recently, transarterial chemoembolization (TACE) was only the standard of care for intermediate-stage HCC. However, first-line lenvatinib followed by locoregional therapy such as selective TACE, resection, or ablation may be a suitable treatment option for intermediate-stage HCC with high tumor burden. pts, patients; LEN, lenvatinib.

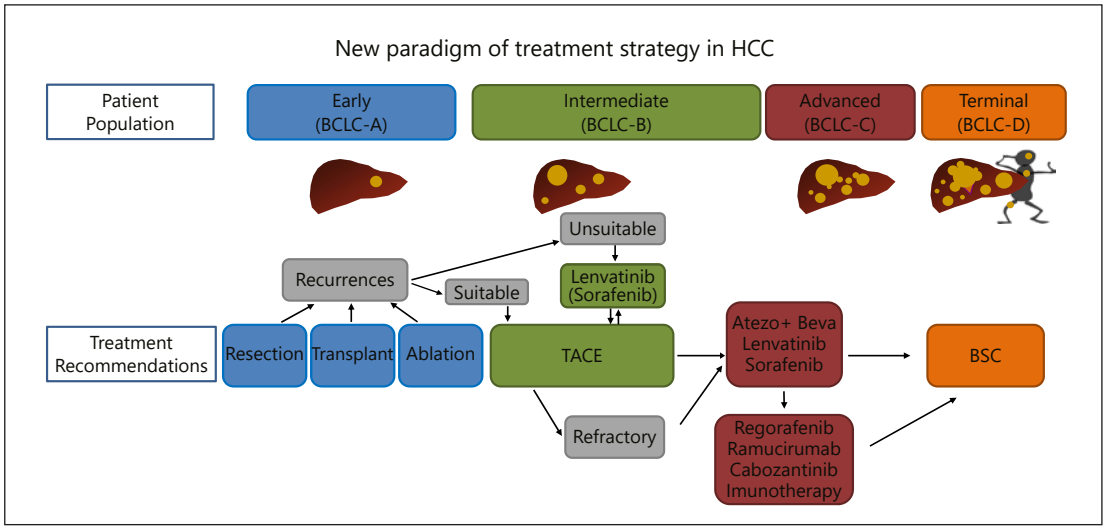

Fig. 2. New paradigm of treatment strategy in HCC. In intermediate-stage HCC, which is unsuitable for TACE, systemic therapy with high response rate such as lenvatinib may be a treatment choice instead of first-line TACE. BCLC-A to -D, Barcelona Clinic liver cancer stages A–D; atezo, atezolizumab; beva, bevacizumab; BSC, best supportive care.

In the TACTICS trial, sorafenib was introduced 2–3 weeks before the first TACE, resulting in normalization of abnormal tumor vessels. This increased the efficacy of TACE by improving the efficiency of drug delivery. In addition, pretreatment with sorafenib might decrease hypoxia-inducible cytokines, such as vascular endothelial growth factor (VEGF) or angiopoietin 2.

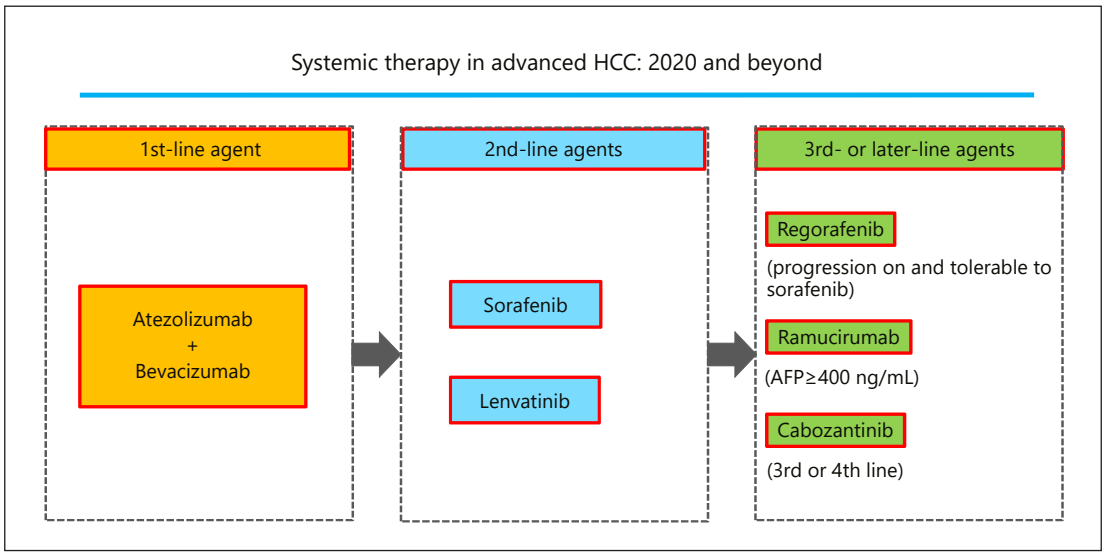

Fig. 3. Systemic therapy in advanced HCC: 2020 and beyond. Success of phase III IMbrave150 trial will bring the atezolizumab plus bevacizumab combination therapy as first-line therapy. AFP, α-fetoprotein.

The concept of TACE-unsuitable HCC has also been gaining attention in recent years [47, 48]. This covers 3 patient types: (1) patients prone to becoming refractory to TACE, (2) patients whose hepatic functional reserve is likely to drop to Child-Pugh B on TACE, and (3) patients basically resistant to TACE [49]. Patients who do not meet the up-to-seven criteria would fall under the first 2 categories [49]. The use of lenvatinib as the initial treatment produces 3 main effects in such patients: it (1) downstages the tumor by inducing necrosis, (2) inhibits progression and metastasis by decreasing the release of VEGF, and (3) increases the effectiveness of TACE by improving the delivery of Lipiodol mixed with anticancer drugs due to normalization of the tumor vasculature. In fact, lenvatinib-TACE sequential therapy significantly extends survival compared with TACE alone in patients who do not meet the up-to-seven criteria [47], and this sequential therapy is gradually becoming the routine approach for TACE-unsuitable patients in Japan [29, 48] (Fig. 1, 2). It is logical that pretreatment with lenvatinib followed by superselective TACE would preserve liver function and increase the response to TACE, improving overall survival compared with nonselective TACE as the first-line treatment for intermediate-stage HCC patients whose tumor burden is beyond the up-to-seven criteria. Among several targeted agents, lenvatinib has the highest overall response rate (41% in the REFLECT trial and 62% [50] in intermediate-stage HCC from the subanalysis of the REFLECT trial). This is better than the overall response rate of TACE, which was 41% in the placebo arm of the world largest TACE combination study, the BRISK-TA trial [41].

Paradigm Change in Advanced HCC

Trends in the use of immune checkpoint inhibitors in patients with advanced HCC have been another major topic of interest recently. Unfortunately, clinical trials of nivolumab as first-line therapy [15] and pembrolizumab monotherapy as second-line therapy [28] both failed. However, there was a successful trial investigating the combination of the anti-PD-L1 antibody atezolizumab with the anti-VEGF antibody bevacizumab, and its results were published in 2020 [17]. The trial was conducted to test the hypothesis that bevacizumab would

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Table 2. Phase II/III clinical trials in early- and intermediate-stage HCC

Target population	Design	Trial name	Result	Presentation	Publication	First author
Early						
Adjuvant (prevention of recurrence)	1. Vitamin K2 vs. placebo	n.a.	Negative	n.a.	Hepatology 2011	Yoshida [55]
	2. Peretinoin vs. placebo	NIK-333	Negative	ASCO 2010	JG 2014	Okita [56]
	3. Peretinoin vs. placebo	NIK-333/K-333	Negative	n.a.	n.a.	n.a.
	4. Sorafenib vs. placebo	STORM	Negative	ASCO 2014	Lancet-O 2015	Bruix [57]
	5. Nivolumab (phase II)	NIVOLVE	Ongoing			
	6. Nivolumab vs. placebo	CheckMate 9DX	Ongoing			
	7. Durvalumab ± bevacizumab vs. placebo	EMERALD-2	Ongoing			
	8. Pembrolizumab vs. placebo	KEYNOTE-937	Ongoing			
	9. Atezolizumab + bevacizumab vs. placebo	IMbrave 050	Ongoing			
Improvement of RFA	1. RFA ± LTLD	HEAT	Negative	ILCA 2013	CCR 2017	Tak [58]
	2. RFA ± LTLD	OPTIMA	Ongoing			
Intermediate						
Improvement of TACE	1. TACE ± sorafenib	Post-TACE	Negative	ASCO-GI 2010	EJC 2011	Kudo [40]
	2. TACE ± sorafenib (phase II)	SPACE	Negative	ASCO-GI 2012	J Hepatol 2016	Lencioni [42]
	3. TACE ± brivanib	BRISK-TA	Negative	ILCA 2013	Hepatology 2014	Kudo [41]
	4. TACE ± orantinib	ORIENTAL	Negative	EASL 2015	Lancet GH 2017	Kudo [43]
	5. TACE ± sorafenib	TACE-2	Negative	ASCO 2016	Lancet GH 2017	Meyer [44]
	6. TACE ± sorafenib (phase II)	TACTICS	Positive	ASCO-GI 2018	Gut 2020	Kudo [45]
	7. TACE + durvalumab ± bevacizumab vs. TACE	EMERALD-1	Ongoing			
	8. TACE + lenvatinib + pembrolizumab vs. TACE	LEAP 012	Ongoing			
	9. TACE + nivolumab ± ipilimumab vs. TACE	CheckMate 74W	Ongoing			
	10. TACE + nivolumab vs. TACE	TACE-3	Ongoing			

RFA, radiofrequency ablation; LTLD, lyso-thermosensitive liposomal doxorubicin; n.a., not applicable. Red, positive trials; blue, ongoing trials; black, negative trials.

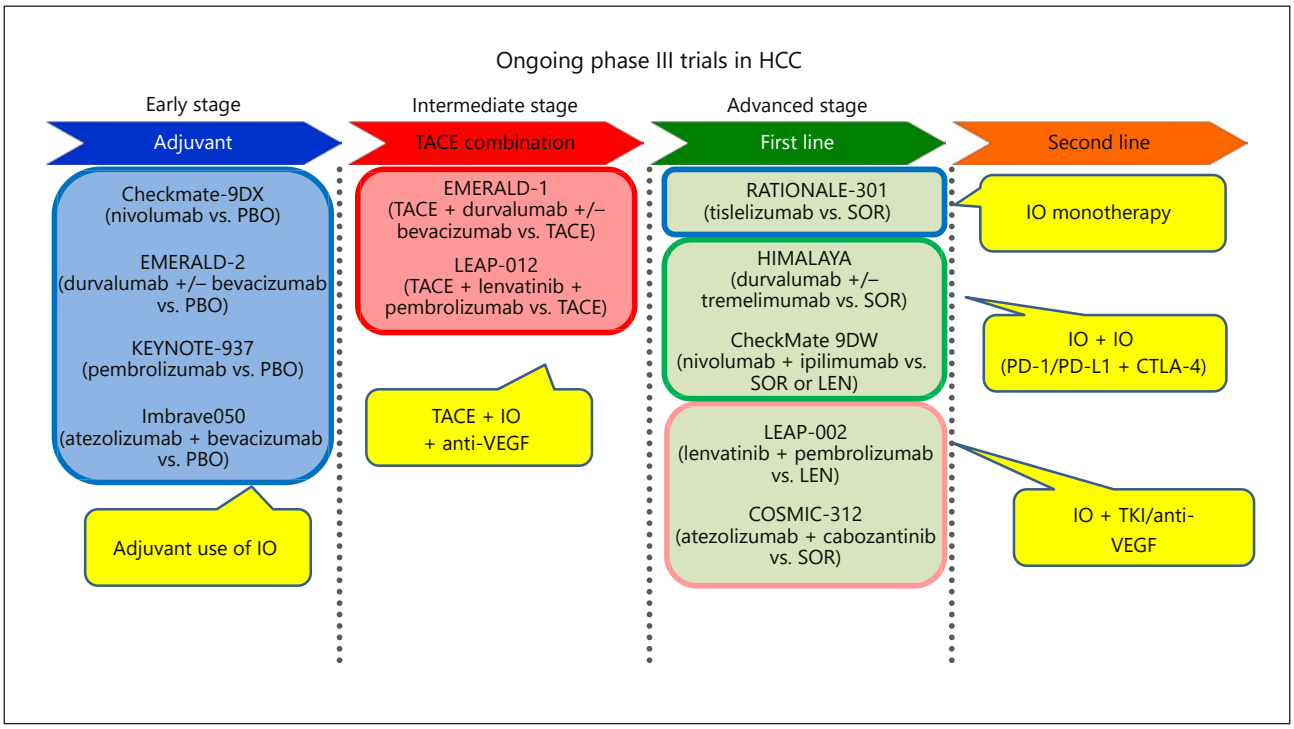

Fig. 4. Ongoing phase III trials in HCC. Several combination trials with immune checkpoint inhibitors are ongoing in early-, intermediate-, and advanced-stage HCC. PBO, placebo; IO, immuno-oncology; SOR, sorafenib; LEN, lenvatinib; VEGF, vascular endothelial growth factor; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; TKI, tyrosine kinase inhibitor.

increase the activation of CD8+ T cells by reversing the immunosuppressive effects of VEGF, which basically induces immunosuppressive cells such as regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells. Thus, atezolizumab plus bavacizumab combination therapy increases cytotoxicity against tumor cells [51–54]. The data generated appear to support this hypothesis. No other systemic treatment option has been shown to extend overall survival compared with sorafenib over the past 12 years, but the first interim analysis for this phase III IMbrave150 trial demonstrated the superiority of the new regimen with respect to both overall survival and progression-free survival [17]. Once combination immunotherapy with atezolizumab and bevacizumab is approved, it seems likely that it will become established as the first-line therapy for advanced HCC (Fig. 3). Currently used drugs will likely be shifted to later lines of treatment (Fig. 3), with first-line drugs (sorafenib and lenvatinib) becoming second-line therapies and current second-line therapies (regorafenib, ramucirumab, and cabozantinib) becoming third-line options. This would represent a marked shift in the paradigm for treatment of advanced HCC.

Ongoing Clinical Trials

Clinical trials of adjuvants for early-stage HCC treated by resection or radiofrequency ablation are ongoing, as are many clinical trials investigating the combination of TACE and an immune checkpoint inhibitor with or without an anti-VEGF antibody (Table 2; Fig. 4) [40–45, 55–58]. Of course, trials investigating monotherapy with immune checkpoint inhibitors and combination therapy with multiple immune checkpoint inhibitors (an anti-PD-1 or PD-L1

antibody plus an anti-CTLA-4 antibody) are ongoing for advanced HCC, as are phase III trials investigating combinations of anti-PD-1/PD-L1 antibodies with tyrosine kinase inhibitors (Table 2; Fig. 4) [4–28]. In other words, trials of immune checkpoint inhibitors are ongoing for all stages of HCC. If these trials succeed, a true paradigm change will occur and treatment outcomes for HCC will be greatly improved.

Preservation of Liver Function Is Essential

It bears repeating that as an increasing number of new effective treatment regimens emerge, there will likely be even greater demand to stop ineffective TACE that decreases the liver function, even though it was once the only treatment recommended by practice guideline for intermediate-stage HCC. The main objective when treating intermediate-stage HCC is to achieve a good response while preserving the hepatic functional reserve. Therefore, when treating patients who are unsuitable for TACE, it is important to stop TACE early or start systemic therapy first followed by selective TACE with curative intent [47, 48], which will both increase the efficacy of TACE and minimize the deterioration of liver function. Preservation of liver function is, therefore, essential for improving treatment outcomes in HCC, and avoiding overuse of TACE is vital in intermediate-stage HCC. The key goal for the treatment of HCC going forward will be preservation of liver function.

In the era of multiple effective systemic therapies, including combination immunotherapy regimens, it will be important to determine how to select the best treatment for a given patient. Expert physicians in the field of HCC management should always keep in mind that preservation of liver function is the most important issue when considering treatment strategies in clinical practice.

Disclosure Statement

Lectures: Eisai, Bayer, MSD, Bristol-Myers Squibb, Lilly, EA Pharma. Grants: Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda, Otsuka, EA Pharma, Abbvie, Eisai. Advisory role: Eisai, Ono, MSD, Bristol-Myers Squibb, Rochep.

Author Contributions

M. Kudo conceived, wrote, and approved the final paper.

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