Sequential Therapy for Hepatocellular Carcinoma after Failure of Atezolizumab plus Bevacizumab Combination Therapy

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Editor *Liver Cancer*

Keywords

Hepatocellular carcinoma · Atezolizumab plus bevacizumab · Lenvatinib · Regorafenib · Ramucirumab

Introduction

The combination of atezolizumab plus bevacizumab has demonstrated marked superiority to sorafenib, the current standard of care for unresectable hepatocellular carcinoma (HCC), with respect to overall survival (OS), progression-free survival (PFS), quality of life, and adverse events [1, 2]. This will undoubtedly lead to atezolizumab plus bevacizumab combination therapy becoming

the first-line therapy of choice from the Fall of 2020. Regarding second-line and later therapies, it is expected, at least theoretically, that current first-line treatments will become second-line treatments, current second-line treatments will become third-line treatments, and so forth [3, 4] (Fig. 1). Because atezolizumab and bevacizumab are antibodies, and their combination is unlikely to affect liver function, it is expected that 70–80% of patients who have started first-line therapy with atezolizumab plus bevacizumab will be eligible for second-line therapy. Thus, the choice of second-line therapy after atezolizumab plus bevacizumab is critical. This Editorial discusses the choice of sequential therapy after failure of atezolizumab plus bevacizumab combination therapy.

Additional Effects of Molecular-Targeted Agents after Immune Checkpoint Inhibitor Therapy

Administration of the anti-PD-1 antibody nivolumab to patients with non-small cell lung cancer results in sustained binding (for about 20 weeks) of nivolumab to PD-1 on lymphocytes [5]. Thus, it is also expected that programmed death-ligand 1 (PD-L1) antibody binding to PD-L1 on cancer cells is sustainable. This suggests that administration of a molecular-targeted agent that inhibits vascular endothelial growth factor (VEGF) as a subsequent therapy for patients with progressive disease treat-

Fig. 1. Systemic therapy for advanced HCC: 2020 and beyond. HCC, hepatocellular carcinoma.

ed with atezolizumab plus bevacizumab may have synergistic effects similar to those of an immune checkpoint inhibitor (ICI) combined with a molecular-targeted agent [6, 7]. Molecular-targeted agents with multi-kinase inhibitory activity, such as lenvatinib, regorafenib, ramucirumab and cabozantinib, are thought to have higher antitumor and tumor-necrosis activity than bevacizumab, which inhibits only a single VEGF-A ligand; thus, they are likely to induce release of more cancer antigens, keep the cancer immunity cycle going, and maintain the effects of remaining any anti-PD-L1 antibodies. Sorafenib (low-dose), lenvatinib, regorafenib, and cabozantinib improve the immune microenvironment by themselves (Fig. 2) [8–13]. Therefore, these molecular-targeted agents may be more effective when administered during the so-called golden time (i.e., the several months during which anti-PD-1/PD-L1 antibody binding is sustained after ICI failure). This is consistent with the feeling that many physicians routinely have during clinical trials or real-world use of anti-PD-1/PD-L1 antibodies, that is, that molecular-targeted agents are more effective when administered after disease progression on ICI therapy. Aoki et al. [14] reported that lenvatinib showed extremely favorable results when used after failure of PD-1/PD-L1 antibody therapy even though it was used as 2nd-, 3rd-, or 4th-line treatment. The objective response rate (ORR) was 55.6%, disease control rate was 86.1%, PFS was 10 months, and

median OS was 15.8 months. Particularly, median OS from the 1st-line treatment was 29.8 months which is much longer than 1st-line lenvatinib (13.6 months) [15] or 1st-line nivolumab (16.4 months) [16] (Table 1). Moreover, as demonstrated by Harding et al. [17], the effects of molecular-targeted agents are independent of WNT/ β -catenin-activating mutations, which means theoretically that these drugs are effective in primary-resistant cases in which ICI was ineffective due to WNT/ β -catenin-activating mutations (Fig. 3).

Potential of Lenvatinib as a Second-Line Treatment after Failure of Atezolizumab plus Bevacizumab

The current expectation is that sorafenib and lenvatinib, the first-line treatments before the advent of atezolizumab plus bevacizumab, will become second-line treatments and that regorafenib, cabozantinib, and ramucirumab will become third-line treatments (Fig. 1). WNT/ β -catenin mutations, which activate β -catenin, are found in approximately 20–30% of all HCCs. The immune classification of HCCs categorizes WNT/ β -catenin mutations into the immune exclusion or immune cold subclasses (Fig. 3) [18–20]. As with other carcinomas (e.g., renal, bladder, and ovarian), HCCs with elevated β -catenin protein levels also show less intratumoral T-cell

Fig. 2. Effect of molecular-targeted agents on the tumor immune microenvironment.

infiltration [21]. However, FGFR4 expression is higher in the population of tumors with WNT/ β -catenin-activating mutations, and there is a positive correlation between β -catenin mutations and FGFR4 expression [22]. It is well known that lenvatinib has a potent inhibitory effect on FGFR4 [23] (Table 2). Yamauchi et al. [22] conducted a study of 40 patients with HCC and reported that lenvatinib achieved a high response rate (81%) in tumors with high expression of FGFR4, which is clearly higher than the corresponding rate in tumors without FGFR4 expression (31%) (Table 3). In addition, treatment with lenvatinib resulted in longer PFS in patients with high FGFR4 expression than in those without FGFR4 expression (5.5 vs. 2.7 months, respectively), indicating that lenvatinib shows higher antitumor activity against tumors with high FGFR4 expression (i.e., tumors with WNT/ β -catenin-activating mutations) (Table 3). Thus, even in patients who do not respond well to previous treatment with atezolizumab plus bevacizumab due to β -catenin-activating mutations, subsequent treatment with lenvatinib would still provide better results due to potent in-

hibitory effect on FGFR4 [24]. In fact, as stated earlier in an ICI trial conducted at our hospital, lenvatinib demonstrated extremely high efficacy in patients who had progressed on previous therapy with a PD-1/PD-L1 checkpoint inhibitor [14]. Specifically, lenvatinib following failure of PD-1/PD-L1 improved PFS (10 months) OS (15.8 months) (from the start of lenvatinib), ORR (55.6%), and disease control rate (86.1%) [14] (Table 1). OS since initiation of ICI therapy was 29.8 months [14] (Table 1), which is much longer than that conferred by lenvatinib alone as first-line therapy [15].

Potential of Sorafenib and Regorafenib as Second-Line Treatments after Failure of Atezolizumab plus Bevacizumab

As noted above, sorafenib, lenvatinib, regorafenib, ramucirumab and cabozantinib alter the immune microenvironment favorably on their own [8]. In particular, sorafenib at low doses improves the immune microenvi-

Table 1. Comparison of efficacy and safety of lenvatinib after PD-1/PD-L1 antibody and REFLECT, CheckMate 459, and IMbrave 150 trials

Study name	Aoki et al. [14]	REFLECT [15]	CheckMate 459 [16]	IMbrave 150 [1]
Treatment	Sequential therapy	Monotherapy	Monotherapy	Combination therapy
Agents	Lenvatinib after PD-1/PD-L1 antibody	Lenvatinib	Nivolumab (subsequent therapy 51%)	Atezolizumab plus bevacizumab
Study design	Retrospective (proof of concept)	Phase III	Phase III	Phase III
Patients, <i>n</i>	36	478	371	336
Treatment line	2-4th line	1st line	1st line	1st line
<i>Efficacy</i>				
ORR (RECISTv1.1), %	22.2	18.8 per IIR	15.0	27.3
ORR (mRECIST), %	55.6	40.6 per IIR	NA	33.2
DCR (mRECIST), %	86.1	73.8 per IIR	NA	72.3
Median PFS, months	10.0	7.4	3.7	6.8
Median OS, months	15.8	13.6	16.4	NE
Median OS from 1st-line initiation, months	29.8	13.6	16.4	NE
Adverse events, %	HT 44 Diarrhea 42 Appetite loss 42 Fatigue 36 AST increase 58 Any grade 100 Grade 3–4 56	HT 42 Diarrhea 39 Appetite loss 34 BW loss 31 AST increase 14 Any grade 99 Grade 3–4 75	Fatigue 11 Pruritus 11 Rash 11 AST increase 11 Appetite loss 6 NA Grade 3–4 22 (TRAE)	HT 30 Diarrhea 19 Fatigue 20 AST increase 20 Any grade 98 Grade 3–4 57

ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; HT, hypertension; IIR, independent imaging review; NA, not available; NE, not evaluable; TRAE, treatment-related adverse event.

Table 2. Comparison of kinase inhibitory effect on targeted molecule between lenvatinib and sorafenib

	IC ₅₀ , nmol/L	
	lenvatinib	sorafenib
VEGFR-1	4.7	21
VEGFR-2	3	21
VEGFR-3	2.3	16
FGFR1	61	340
FGFR2	27	150
FGFR3	52	340
FGFR4	43	3,400
PDGFRα	29	1.6
PDGFRβ	160	27
RAF1	1,610	46.4
BRAF	8,660	314

VEGF, vascular endothelial growth factor. Bold character represents an inhibitory effect on each molecule. Modified from ref. [24].

Table 3. Efficacy of lenvatinib on FGFR4 positive HCC (*n* = 40)

	FGFR4-ICH positive, <i>n</i> = 27	FGFR4-IHC negative, <i>n</i> = 13
CR, <i>n</i>	0	0
PR, <i>n</i>	22	4
SD, <i>n</i>	3	4
PD, <i>n</i>	2	5
ORR, %	81	31
DCR, %	93	62
PFS, months	5.5	2.5

IHC, immunohistochemical staining; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; HCC, hepatocellular carcinoma. Modified from ref. [22].

Fig. 3. Immunological classification and possible treatment strategies. VEGF, vascular endothelial growth factor; HCC, hepatocellular carcinoma; MDSC, myeloid-derived suppressor cell.

ronment as revealed in a systemic review of the in vivo and in vitro study [25] that lower dose of sorafenib is associated with beneficial immunomodulatory effect, such as increasing the M1 polarization of tumor-associated macrophages (TAMs) [26, 27] enhancing CD8⁺ T-cell infiltration and function [28–30] suppressing regulatory T-cell numbers [31–33] or reversing the function of myeloid-derived suppressor cells in the tumor microenvironment [8, 9, 25] (Fig. 2). On the other hand, it is suggested that higher dose of sorafenib has immunosuppressive effect through induction of hypoxia and recruitment of myeloid-derived suppressor cells, TAM, or other suppressive cells [8, 11–13, 25, 34–37] (Fig. 2). Regorafenib also suppresses TAMs, induces M1 macrophage activation, and increases CD8-positive cell numbers [8]. Meanwhile, osteopontin induces TAMs via colony-stimulating factor-1 (CSF-1), thereby exerting a suppressive regulatory effect on the tumor immune microenvironment and inhibiting infiltration of CD8-positive cells into

the tumor [38]. Experimental study of both CSF-1 receptor (CSF-1R) inhibitors and anti-PD-L1 antibodies to tumors leads to significantly higher numbers of CD8-positive and CD4-positive cells, and significantly lower numbers of TAMs, than in controls [38]. These observations suggest that inhibiting CSF-1R suppresses tumor infiltration by TAMs, thereby enhancing PD-L1 inhibition [38]. Thus, as shown in Figure 4, CSF-1R inhibitors should theoretically increase intratumoral infiltration of CD8-positive and CD4-positive cells by inhibiting TAMs and M2 macrophages, and exert a potent antitumor effect when combined with anti-PD-1/PD-L1 antibodies.

Moreover, increased TAM infiltration plays an important role in acquired resistance to anti-VEGF therapy. Therefore, it is assumed that use of CSF-1R inhibitors in patients that have acquired resistance will allow tumor cells to regain sensitivity to anti-VEGF therapy (Fig. 5) [39]. Thus, CSF-1R inhibitors may be effective in patients that do not respond to atezolizumab plus bevacic-

Fig. 4. CSF-1R inhibitors change tumor microenvironment from immune suppressive of immune responsive. CSF-1R, colony stimulating factor 1 receptor; TAM, tumor-associated macrophage. Modified from ref. [38].

Table 4. Pharmacological inhibitory kinase activity of regorafenib and its metabolites

Gene symbol	K_d , nmol/L		
	regorafenib*	M-2	M-5
VEGFR-2	57/28	29	31
PDGFRA	21/19	7.3	11
PDGFRB	19/8.3	11	11
KIT	35/6.9	9.8	5.8
RET	7.7/5.2	7.6	5.8
CSF1R	43/10	21	13
FLT3	9.6/4.8	6.7	2.6
RAF1	87/59	130	66
BRAF	42/52	24	17

M-2, M-5: metabolites of regorafenib. * Duplicate K_d values are given.

zumab due to resistance to bevacizumab. In fact, regorafenib suppresses CSF-1R through its kinase activity (Table 4) [40]; thus, it may be effective at improving the immunosuppressive microenvironment. The well-known effects of regorafenib include (1) inhibiting angiogenesis in the vascular endothelium; (2) inhibiting cancer extension; (3) inhibiting metastatic activity; and (4) inhibiting CSF-1R, which in turn strengthens immunity [40–45]. Studies in a mouse model of HCC show that low-dose regorafenib induces activated CD8-positive cells while at the same time significantly reducing the number of TAMs; it also decreases M2 macrophage numbers while significantly increasing those of M1 macrophages [46]. These results suggest that regorafenib significantly alters the immune microenvironment, changing it from suppressive to responsive. Therefore, regorafenib, which has such a promising effect, may also be effective as a second-line treatment when administered at low doses after failure of atezolizumab plus bevacizumab, particularly for HCCs that have progressed due to resistance to bevacizumab.

Fig. 5. Effect of CSF1R inhibitor on acquired resistance to anti-VEGF therapy for cancer. VEGF, vascular endothelial growth factor. Modified from ref. [39].

Potential of Other Molecular-Targeted Agents as Subsequent Therapy after Failure of Atezolizumab plus Bevacizumab

As mentioned above, binding of anti-PD-1 antibodies to PD-1 on lymphocytes and of anti-PD-L1 antibodies to PD-L1 on cancer cells is expected to last for more than 20 weeks [5]. Therefore, in general terms, molecular-targeted agents as second-line treatment after failure of PD-1/PD-L1 antibodies are considered to be as effective as combination therapy with ICIs plus anti-VEGF/molecular-targeted agents. Moreover, if the effect of anti-PD-L1 antibodies lasts for several months, then sequential therapy with agents with antitumor activity stronger than that of bevacizumab (i.e., lenvatinib, sorafenib, regorafenib, ramucirumab and cabozantinib) would be more effective.

Furthermore, and from a different perspective, ramucirumab may be a candidate for second-line therapy when serum AFP level is ≥ 400 ng/mL. Since ramucirumab does not impair liver function and quality of life [47, 48], its use as a second-line treatment after atezolizumab plus bevacizumab may offer patients a better quality of life, with fewer adverse events, while maintaining stable dis-

ease even in elderly patients. Furthermore, recent report by Finn et al. [49] showed that ramucirumab achieved ORR of 16.7% (4 of 24 cases) in patients who failed prior PD-1/PD-L1 antibody therapies (nivolumab in 3 and durvalumab plus tremelimumab in 1) in the REACH-2 Open-Label Expansion Cohort, suggesting that ramucirumab may be effective after ICI therapy. Therefore, there may be cases in which it is appropriate to give this drug as a “short break” (e.g., in elderly patients and patients with poor PS). In any case, the efficacy of these drugs as second-line treatments after failure of atezolizumab plus bevacizumab therapy should be evaluated in real-world clinical practice.

Conclusion

The current expectation is that sorafenib and lenvatinib, both first-line treatments before the advent of atezolizumab plus bevacizumab [1, 50], will become second-line treatments and that regorafenib, cabozantinib, and ramucirumab will become third-line treatments (Fig. 1). At present, lenvatinib is likely to be the most fa-

avorable second-line treatment and is theoretically expected to provide a higher response rate, longer PFS and OS than other targeted agents since its effectiveness on FGFR4 overexpressed (WNT/ β -catenin mutated) HCC. Actually, in our study, lenvatinib treatment after failure of PD-1/PD-L1 antibody therapy provided much better outcomes than lenvatinib alone or nivolumab alone as the first-line therapy [14] (Table 1). For third-line and later therapies, a variety of agents will be used in a variety of sequences.

However, as mentioned above, regorafenib [51], cabozantinib [52], and ramucirumab [53, 54] were proved to prolong overall survival by clinical trials; thus, they may be used as second-line treatments after atezolizumab plus bevacizumab in some cases. In light of this, the question of which sequence is best will have to be addressed in real-world clinical settings. Through such studies, it will be increasingly important to clarify the actual status of sequential therapy use after failure of atezolizumab plus bevacizumab combination therapy.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

Lectures: Eisai, Bayer, Chugai and MSD; grants: EA Pharma, Eisai, Gilead, Takeda, Otsuka, Eli Lilly, Chugai, and Taiho; advisory consulting: Eisai, Ono, MSD, Eli Lilly, Roche, Takeda, and BMS. Masatoshi Kudo is Editor-in-Chief of Liver Cancer.

Funding Sources

The authors did not receive any funding.

Author Contributions

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

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