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Review

Transarterial chemoembolization in combination with programmed death-1/programmed cell death-ligand 1 immunotherapy for hepatocellular carcinoma: A mini review

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. With the development of systemic therapies, several studies are currently underway, especially those related to the use of programmed death-1/programmed cell death-ligand 1 (PD-1/PD-L1) immunotherapy. Moreover, studies on transarterial chemoembolization (TACE) and PD-1/PD-L1 immunotherapy have demonstrated some interesting outcomes. This article reviewed the current clinical evidence on the combination of TACE and PD-1/PD-L1 immunotherapy. Overall, our review summarized that a favorable survival time could be achieved using this combination in most patients. However, complications such as hyperprogression should be taken seriously, and the underlying mechanisms need to be explored.

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide, with more than 840,000 newly diagnosed cases annually [1]. The incidence of HCC varies among different regions and individuals, and more than 30%–50% of newly diagnosed cases have been reported in China; remaining cases are reported mainly in Europe, North America, and Latin America [2]. In addition, a variety of etiologies, including hepatitis B virus, hepatitis C virus, nonalcoholic fatty liver disease, alcoholic liver disease, and unknown etiologies have been associated with HCC and liver cirrhosis; therefore, the etiological heterogeneity of HCC acts as a hurdle when treating this condition [3]. At an early stage, most patients with HCC are asymptomatic, which delays the diagnosis, resulting in the progression of HCC to aggressive stage with significant symptoms. Currently, clinical guidelines and experts' consensus have recommended many treatments, such as hepatectomy, liver transplantation, and locoregional, interventional, and systemic therapies [4–6]. However, treatments for HCC are mainly based on the tumor stage, and systemic therapies are recommended for patients with intermediate/advanced-stage HCC (BCLC-B or C) [7]. In patients with intermediate/advanced-stage HCC, the treatment options are limited due to liver dysfunction, metastasis, and other unideal conditions; therefore, interventional and systemic therapies play an essential role in treating this condition [8,9]. Patients in the BCLC-B stage exhibit symptoms like multiple lesions and preserved liver function; however, patients in the BCLC-C stage exhibit portal vein invasion and/or extrahepatic metastasis [10]. Accordingly, the treatment protocols for HCC should consider the factors mentioned above and the disease background of patients with

Abbreviations: HCC, Hepatocellular carcinoma; TACE, Transarterial chemoembolization; OS, Overall survival; PFS, Progression-free survival; ICI, Immune checkpoint inhibitor; TKI, Tyrosine kinase inhibitor; AE, Adverse event.

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HCC; therefore, the management of HCC should be carefully evaluated.

With the development of systemic therapy, many oral drugs, such as sorafenib and lenvatinib, are recommended in the first-line or second-line settings for patients with HCC by recommended guidelines. Donafenib (an analog of sorafenib) [11,12], nivolumab [13], pembrolizumab [14,15], and bevacizumab [16–18] have proved to be effective in treating intermediate/advanced-stage HCC. Besides, multiple immune checkpoint inhibitors (ICIs) are adopted as second-line or third-line therapies [19]. The mechanism underlying cancer immunotherapy differs considerably from other cancer treatment approaches. Anti-programmed cell death protein (PD)-1/ligand (PD-L1) antibodies may have a significant impact on the microenvironment of HCC and induce cytotoxic T cell-mediated destruction of HCC [20]. Studies have shown that the memory T cells express CD4/CD8 in tumor response and express biomarkers such as PD-1. In mouse models, a T-cell population like the short-term memory T cells has also been found in tumor-bearing animals [21]. As expected, the PD-1/PD-L1 inhibitors blocked the priming of naive T cells. There was a transient accumulation of tumor-infiltrating lymphocytes expressing CD4/CD8, exhibiting lower levels of PD-1, indicating that these cells were higher in number than the T cells from control tumors [22]. Therefore, PD-1/PD-L1 immunotherapy might play an essential role in cancer immunology. Clinical studies demonstrated that PD-1/PD-L1 immunotherapy could reach a favorable response rate in patients with HCC [23,24]. The IMbrave 150 study demonstrated that atezolizumab and bevacizumab led to significantly improved overall survival (OS) and progression-free survival (PFS) compared with sorafenib in patients with advanced HCC at the primary analysis (after a median of 8.6 months of follow-up). However, the long-term outcome is still under investigation [25]. Based on the above-mentioned clinical evidence, although some treatments of PD-1/PD-L1 immunotherapy and other immunotherapies are under clinical investigation, some ideal outcomes have been reported in patients with HCC [26].

Transarterial chemoembolization (TACE), an approach that embolizes the hepatic artery of HCC, is a standard treatment option for intermediate-stage HCC. Besides, TACE involves the use of anticancer drugs, such as lobaplatin and fluorouracil, which provide high local drug concentrations in tumor growth areas. Besides, TACE also can be applied as a short-term treatment for patients with HCC waiting for a liver transplant [27]. TACE is recommended as the standard treatment for BCLC-B stage HCC [28]. Besides, according to some eastern HCC guidelines or experts' consensus, TACE can also be performed for some patients in the BCLC-C stage with preserved liver function [29]. While real-world evidence is increasing, some studies have made broad conclusions about TACE in combination with PD-1/PD-L1 immunotherapy. Most studies found that this combination is promising for intermediate/advanced-stage HCC. This review aimed to collect current evidence of TACE in combination with PD-1/PD-L1 immunotherapy for HCC.

2. Methods

We searched the PubMed and Embase databases for literature in July 2022 to select relevant studies on TACE in combination with PD-1/PD-L1 immunotherapy for HCC. We only included studies published in English, and case reports were not considered. Besides, because of the narrative nature of our review, studies with different designs were included and discussed; therefore, the PRISMA guidelines were not given. Table 1 shows the search strategy summary. Figure 1 shows the flowchart of the study selection.

3. Clinical evidence of TACE in combination with PD-1/PD-L1 immunotherapy for HCC

Breakthroughs regarding TACE in combination with PD-1/PD-L1 immunotherapy have been made in the past years since nivolumab, camrelizumab, pembrolizumab, durvalumab, and sintilimab were included as new systemic drugs for advanced HCC [5]. Clinical studies that investigated the combination of TACE and PD-1/PD-L1 immunotherapy are shown in Table 2 [30–52]. The overwhelming majority of studies were retrospective with this study (n = 21), and the period ranged from 2021 to 2022. A large portion of the cohort population consisted of patients from Asia, as twenty-two studies were from China, and one was from the USA. Although it is too early to conclude the effect of combination of TACE and PD-1/PD-L1 immunotherapy on HCC, as many clinical studies are still under investigation, those studies may provide new methods for treating HCC in the future. After a comprehensive research of databases, we found that fourteen studies used camrelizumab in combination with TACE with tyrosine kinase inhibitors (TKIs). Besides, current evidence shows that the therapeutic effect of TACE in combination with camrelizumab and TKIs is superior to TACE in combination with camrelizumab.

Studies investigating the effect of immunomodulators in the tumor microenvironment demonstrated that PD-1/PD-L1 inhibitors block the co-inhibitory signals and unlock the negative regulation of the immune response [53,54]. Malignancy tends to have more mutations that function as neoantigens, increased PD-1-positive lymphocytic infiltration, and greater PD-L1-expression on tumor cells [55,56]. Besides, ICIs have been developed for different kinds of malignancies. The rationale for combination therapy of TACE and PD-1 inhibitors may be explained by the fact that HCC necrosis from TACE is associated with the release of tumor neoantigens, and PD-1 inhibitors add to the immune recognition and activation of those neoantigens [4]. Studies have confirmed that chemotherapy boosts the exposure of tumor cells to antigens, which is conducive to the immune effect of ICIs and enhances antitumor efficacy. Moreover, PD-1/PD-L1 inhibitors may be promising for combination therapy with antiangiogenic drugs because the significant toxicity effects of TKIs and ICIs do not overlap. There may be synergistic biological effects between TKIs and ICI agents [57].

Camrelizumab, a PD-1/PD-L1 inhibitor available in China since May 2019, is the most commonly used PD-1 inhibitor in combination with

Table 1
Search strategy summary.

Search item	Specification
Time span	Jan 1, 1980, to Jun 28, 2022
Databases and other sources searched	PubMed database and references citation tracking
Search terms used	#1 hepatocellular carcinoma [Mesh Terms] #2 unresectable hepatocellular carcinoma [Title/Abstract] #3 advanced hepatocellular carcinoma [Title/Abstract] #4 primary liver cancer [Title/Abstract] #5 #1 OR #2 OR #3 OR #4 #6 TACE [Title/Abstract] #7 transarterial chemoembolization [Mesh Terms] #8 #6 OR #7 #9 immunotherapy [Title/Abstract] #10 nivolumab [Title/Abstract] #11 pembrolizumab [Title/Abstract] #12 PD-1 [Title/Abstract] #13 PD-L1 [Title/Abstract] #14 atezolizumab [Title/Abstract] #15 bevacizumab [Title/Abstract] #16 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #17 humans [Mesh Terms] #18 #5 AND #8 AND #16 AND #17
Inclusion and exclusion criteria	Inclusion Articles reporting on TACE in combination with PD-1/PD-L1 immunotherapy Malignancies in patients who underwent surgery, available in English. Articles must provide survival information. Exclusion Guidelines, case report, thesis and editorial reviews. HAIC and other interventional therapies.
Selection process	Tow reviewers selected studies.

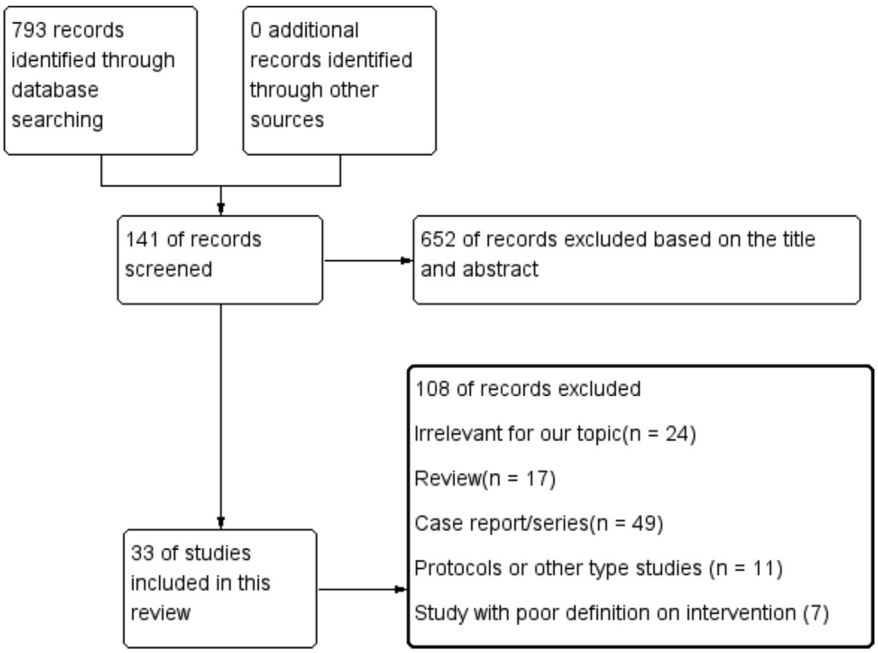

Fig. 1. Flowchart of study selection.

TACE. Qin S et al. [58] reported that camrelizumab alone for patients with advanced HCC showed a median OS of 13.8 months, which is promising compared to the current clinical trials. Camrelizumab can bind PD-1 and PD-L1, activating the T cells to achieve its antitumor effect. Besides, camrelizumab has also been applied in different types of cancer, including HCC and other malignancies [59–61]. It should also be noticed that Guo Y et al. reported that TACE, in combination with camrelizumab, had a similar OS on patients with recurrent HCC compared with TACE alone. However, combination therapy may provide a longer PFS (nine months vs. six months), which indicates that TACE might be a better option for patients with recurrent HCC. Ren Y et al. [36] reported that compared with conventional TACE in combination with PD-1/PD-L1 immunotherapy, drug-eluting beads TACE and PD-1/PD-L1 immunotherapy inhibitors might bring better PFS (ten months vs. three months) and tumor response (disease control rate: 70.4% vs. 40.7%). However, the authors did not report the OS between groups. Xiang Y et al. [33] reported that TACE, along with camrelizumab, sintilimab, and lenvatinib, showed the most exciting results of OS (HR = 0.27, 95% CI: 0.104–0.704) compared with TACE and camrelizumab and sintilimab without lenvatinib in patients with BCLC stage B HCC. These studies provided a rationale for using ICIs and TKIs based on TACE.

Sintilimab is a PD-1 monoclonal antibody [62]that has been available in China since 2019. Xie D et al. [52] reported the results of sintilimab along with TKIs and TACE in patients with multinodular HCC or locally advanced HCC with portal vein tumor thrombus. They revealed that the patients from the combination group tended to have a longer PFS (median, 10.1 vs. 9.1 months, $p = 0.73$) than those from the non-TACE group but without significant differences. Similarly, Menglong Zhang et al. [31] reported that the overall response rate and disease control rate of the combination group were 77.4% and 93.5%, respectively, at 3 months and were higher than those of the TACE group ($p < 0.05$). Xiang Y et al. reported that compared to TACE plus sintilimab without lenvatinib group in treating patients with HCC at BCLC-B stage, the TACE plus sintilimab with lenvatinib group showed a significantly higher PFS (PFS 22.5 months vs. 14.0 months, $p < 0.001$). Similar results were obtained in terms of OS (hazard ratio = 0.270, 95% CI = 0.104–0.704). Cao F et al. [49] conducted a single-arm study in which TACE combined with lenvatinib plus sintilimab achieved a median OS of 23.6 months and median PFS of 13.3 months, and duration of response was 10 months, which indicated that TACE combined with lenvatinib plus sintilimab could be a promising therapeutic regimen for unresectable HCC.

Besides, combination therapy of TACE and PD-1/PD-L1 inhibitors, such as nivolumab [41], pembrolizumab [36,39,48,51], and toripalimab [35,36,39,43,51] showed a promising outcome in patients with HCC regardless of the tumor stage. These exciting results gave clinicians more choices while treating HCC, even when drug resistance occurred.

Interestingly, the studies mentioned above have shown that combination therapy of TACE and PD-1/PD-L1 immunotherapy with TKIs showed the best outcome. Jain RK found that TKIs may enhance the therapeutic effect of PD-1 inhibitors and vice versa [63]. As the monotherapy of ICIs or TKIs exhibited limited efficacy, the objective response rate of 9.2% in sorafenib [64], 24.1% in lenvatinib [64], and 17% in crembrolizumab [65] for HCC. On the bias of these clinical studies, we found that TACE plus TKIs with immunotherapy may be the first choice for most unresectable HCC and provide the potential synergetic effect for patients with HCC. Even anti-PD-L1 inhibitors, such as durvalumab, avelumab, and atezolizumab, and anti-CTLA-4 inhibitors, such as ipilimumab and tremelimumab are reported in some clinical studies and preclinical studies. Moreover, no clinical studies have reported the combination of anti-PD-L1/anti-CTLA-4 inhibitors, such as durvalumab, avelumab, and atezolizumab plus TACE for HCC, and further studies are required for detailed exploration. Additionally, most of the mentioned studies were not randomized controlled studies, and those studies have a known limitation: they focus more on the benefits than the harms [66].

Furthermore, the mechanism of PD-1/PD-L1 immunotherapy and other immunotherapies still needs to be discovered, and large-simple, high-quality, and multi-center randomized trials are required to investigate the long-term effects of immunotherapy with or without TACE.

4. Ongoing studies of TACE in combination with PD-1/PD-L1 immunotherapy

Currently, many studies have been performed demonstrating the effect of TACE in combination with immunotherapy. TACE and PD-1/PD-L1 immunotherapy combination protocols, such as durvalumab and pembrolizumab, are under clinical investigation, which may add more options for clinical practice. Ongoing studies of TACE in combination with immune therapies are shown in Table 3.

Table 2
Summary of clinical studies on TACE in combination with PD-1/PD-L1 immunotherapy for HCC.

Study	Region/ country	Study design	Number of patients (I/C)	Intervention	Control	Follow-up (months)	Overall survival [HR (95% CI)]
Sujing Zhang 2022 [30]	China	Prospective, randomized	46/46	TACE: 0.75 g fluorouracil and 100 mg oxaliplatin, emulsion of 20 mg lipiodol and 20 mg epirubicin. PD-1/PL-L1: camrelizumab 200 mg once every 21 days.	TACE: 0.75 g fluorouracil and 100 mg oxaliplatin, the emulsion of 20 mg lipiodol and 20 mg epirubicin.	From 7 to 24 months, with a median duration of 12 months.	NR
Menglong Zhang 2022 [31]	China	Retrospective cohort study	31/31	TACE: 20–40 mg lobaplatin, 20–40 mg epirubicin mixed with 10 ml of poppy lipiodol. PD-1/PL-L1: sintilimab: 200 mg every 3 weeks. TKI: Lenvatinib 12 mg/d (weight ≥60 kg) or 8 mg/d (weight <60 kg).	TACE: 20–40 mg lobaplatin, 20–40 mg epirubicin mixed with 10 mL of lipiodol.	All 62 patients completed a 2-year follow-up, and the follow-up span was 30 months.	NR
Jin-Xing Zhang 2022 [32]	China	Single-arm retrospective study	38	TACE: lobaplatin 30–50 mg, epirubicin 10–30 mg, infused. PD-1/PL-L1: camrelizumab 3 mg/kg every 3 weeks or every 4 weeks. TKI: apatinib 250 mg per day.	NA	NR	NA
JinXing Zhang 2022 [33]	China	Single-arm retrospective study	34	TACE:lobaplatin 30–50 mg, emulsion 10 mg epirubicin and 10 mL Lipiodol. PD-1/PL-L1: 3 mg/kg camrelizumab every 3 or 4 weeks.	NA	10.6 months (range: 2.4–25.0 months	NA
Fei Yang 2022 [34]	China	Single-arm retrospective study	53	TACE: lipiodol THP 10–20 mg; lipiodol less than 30 mL, gelatin sponge or polyvinyl alcohol particles 300–500 mm. PD-1/PL-L1: camrelizumab 200 mg every 3 weeks. TKI: sorafenib 800mg/lenvatinib 8 mg or 12 mg orally daily.	NA	From August 1, 2019, to March 30, 2021	NA
Yan-Jun Xiang 2022 [35]	China	Retrospective cohort study	56/47	TACE: doxorubicin hydrochloride, pirarubicin or pharmorubicin and lipiodol, Gelfoam fragments. TKI: Lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: toripalimab 3 mg/kg, sintilimab 200 mg every three weeks.	TACE: 20–40 mg lobaplatin, 20–40 mg epirubicin, 10 ml poppy lipiodol. PD-1: sintilimab 200 mg every 3 weeks. PD-1: toripalimab 3 mg/kg, sintilimab 200 mg every three weeks.	Median follow-up for the entire cohort was 11.4 months	0.27 (0.104, 0.704)
Jia-Yi Wu 2021 [36]	China	Single-arm retrospective study	62	TACE: iodized oil and pirarubicin were mixed, with gelatin sponge particles. TKI: Lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: sintilimab 200 mg, tislelizumab 200 mg, camrelizumab 200 mg, toripalimab 240 mg, or pembrolizumab 200 mg once every 3 weeks.	NA	Median follow-up of 12.2 months (range, 7.6–33.3 months	NA
Ying Teng 2022 [37]	China	Single-arm retrospective study	53	TACE: epirubicin 50 mg and lipiodol 5–20 ml, absorbable biosphere microspheres 300–500 mm. TKI: Lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: camrelizumab or sintilimab 200 mg 21-day cycle.	NA	NR	NA
Yanqiao Ren 2022 [38]	China	Retrospective study	27/27	TACE: lipiodol 10–20 mL and epirubicin 10–30 mg emulsion, 500-700μ absorbable gelatin sponge particles. PD-1/PL-L1: camrelizumab: 200 mg every 3 weeks.	DTACE: 100–300 μm chemoembolization reagent carriers and agents, epirubicin 20 mg/Ml. PD-1: camrelizumab: 200 mg every 3 weeks.	11.0 months (range,3–16 months)	NR
Shuping Qu 2022 [39]	China	Prospective cohort study	56/54	TACE: pirarubicin emulsified with iodized oil, absorbable gelatin sponge particles. TKI: lenvatinib: 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: pembrolizumab 200 mg or toripalimab 240 mg every three weeks.	TACE: pirarubicin emulsified with iodized oil, absorbable gelatin sponge particles.	Median duration of follow-up was 21.3 months (range, 9.3–38.5)	0.23 (0.12,0.42)

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Table 2 (*continued*)

Study	Region/ country	Study design	Number of patients (I/C)	Intervention	Control	Follow-up (months)	Overall survival [HR (95% CI)]
Jian Qin 2022 [40]	China	Retrospective cohort study	25/41	TACE:20–80 mg pirarubicin/ epirubicin, 10–50 mg loplatin, 3–6 mg raltetrexed, 6–20 mL iodide oil. PD-1/PL-L1: sintilimab or camrelizumab; 200 mg every 21 days. TKI: Sorafenib 400 mg twice daily.	TACE:20–80 mg pirarubicin/ epirubicin, 10–50 mg loplatin, 3–6 mg raltetrexed, 6–20 mL iodide oil. PD-1: sintilimab or camrelizumab; 200 mg every 21 days;	The median follow-up time was 8.5 months.	NR
Brett Marinelli 2022 [41]	USA	Retrospective multicenter study	155/31[a]	PD-1/PL-L1: Nivolumab 3 mg/kg or 240 mg every 2 weeks, or 480 mg every 4 weeks. TACE: doxorubicin and lipiodol or drug-eluting radiopaque microbeads.	PD-1: Nivolumab 3 mg/kg or 240 mg every 2 weeks, or 480 mg every 4 weeks.	Median:9.3 (IQR 4.0–16.4)	0.55 (0.26,1.17)
Juanfang Liu 2021 [42]	China	Single-arm retrospective study	22	TACE: raltitrexed 4 mg, oxaliplatin 100 mg, 10–20 mL lipiodol and 20 mg pirarubicin. TKI: Lenvatinib 12 mg/day body weight≥60 kg or 8 mg/day f < 60 kg. PD-1/PL-L1: camrelizumab 200 mg every 3 weeks.	NA	NA	NA
Xiaowei Li 2022 [43]	China	Single-arm retrospective study	114	TACE: pirarubicin and lipiodol, gelatin sponges TKI: lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: camrelizumab 200 mg, toripalimab 240 mg, sintilimab 200 mg or tislelizumab 200 mg every 3 weeks.	NA	Median follow-up duration of 10.6 months 8.5–12.8.	NA
Shuguang Ju 2022 [44]	China	Retrospective cohort study	52/56	TACE: 1)drug-eluting bead loaded with 60 mg doxorubicin; 2)iodine oil–doxorubicin emulsion, absorbable gelatin-sortable sponge particles. PD-1/PL-L1: camrelizumab 200 mg every 3 weeks. TKI: apatinib 250 mg/day.	PD-1: camrelizumab 200 mg every 3 weeks. TKI: apatinib 250 mg/day.	Median follow-up time was 13.5 months.	0.41 (0.22,0.77)
Shuguang Ju 2022 [45]	China	Single-arm retrospective study	80	cTACE: iodine oil, doxorubicin emulsion, 350–560 μm absorbable gelatin sponge. DEB-TACE, CalliSpheres loaded with 60 mg of doxorubicin. PD-1/PL-L1: camrelizumab 200 mg every 3 weeks. TKI: apatinib 250 mg/day.	NA	Median OS was 22.1 months (95% confidence interval [CI]: 13.8–30.5 months)	NA
Yun Huang 2022 [46]	China	Retrospective case series	13	TACE: supra-selective injection of lipiodol with cisplatin. Radiotherapy: a total of 36–42 Gy in 4–5 fractions. TKI: Sorafenib 400 mg twice per day. PD-1/PL-L1: camrelizumab 200 mg every 3 weeks.	NA	NA	NA
Yusheng Guo 2022 [47]	China	Retrospective cohort study	20/51	TACE: 2–20 mL lipiodol, 20–60 mg epirubicin, gelatin sponge particles 350–710 μm. PD-1/PL-L1: camrelizumab 200 mg every 3 weeks.	TACE: 2–20 mL lipiodol, 20–60 mg epirubicin, gelatin sponge particles 350–710 μm.	Median follow-up period was 12 months (range, 4–55 months)	NR
Song Chen 2022 [48]	China	Retrospective cohort study	70/72	DTACE: microspheres or drug-eluting beads, absorbable gelatine sponge. PD-1/PL-L1: pembrolizumab 200 mg once every 3 weeks. TKI: Lenvatinib: 8 mg/day.	DTACE: microspheres or drug-eluting beads, absorbable gelatine sponge. TKI: Lenvatinib: 8 mg/day.	Median duration of follow-up was 27 months (95% CI 26.3–28.7 months)	0.56 (0.38, 0.83)
Fei Cao 2021 [49]	China	Retrospective multicenter center study	52	TACE: Oxaliplatin 75 mg/m^2 infusion; iodized oil mixed with epirubicin 30–50 mg/m^2 embolization; TKI: Lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: sintilimab 200 mg 21-day therapy cycle.	NA	Median:12.5 (9.1–14.8)	NA

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Table 2 (*continued*)

Study	Region/ country	Study design	Number of patients (I/C)	Intervention	Control	Follow-up (months)	Overall survival [HR (95% CI)]
Mingyue Cai 2022 [50]	China	Retrospective cohort study	41/40	cTACE: 5–20 mL Lipiodol, 20–60 mg pirarubicin, polyvinyl alcohol particles 90–500 mm. DTACE: CalliSpheres or DC Bead 100–300 mm loaded with 60 mg pirarubicin. TKI: Lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: Sintilimab or camrelizumab 200 mg once every 3 weeks.	cTACE: 5–20 mL Lipiodol, 20–60 mg pirarubicin, polyvinyl alcohol particles 90–500 mm. DTACE: CalliSpheres or DC Bead 100–300 mm loaded with 60 mg pirarubicin. TKI: Lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily.	Follow-up duration ranged from 4.6 to 29.8 months, with a median of 13.7 months.	NR
Yun Zhu 2021 [51]	China	Retrospective cohort study	39/72	HAIC, TACE TKI: lenvatinib 12 mg (≥60 kg) or 8 mg (<60 kg) once daily. PD-1/PL-L1: toripalimab 240 mg, camreli-zumab 200 mg, sintilimab 200 mg, tislelizumab 200 mg, pembrolizumab 2 mg/kg, every 3 weeks.	Lenvatinib: 12 mg (≥60 kg) or 8 mg (<60 kg) once daily.	NA	
Diyang Xie 2021 [52]	China	Retrospective single-center study	14	TACE: NA. TKI: sorafenib or Lenvatinib or regorafenib or apatinib; PD-1/PL-L1: sintilimab 200 mg every 3 weeks.	NA	Median:10.4 (4.3–23.9)	NA

I: interventional group; C: control group; TACE: transarterial chemoembolization; PD-1: programmed death 1; PD-L1: programmed cell death ligand 1; NR: not reported; TKI: tyrosine kinase inhibitors; NA: not available; DTACE: drug-eluting beads transarterial chemoembolization; HR: hazard ratio; CI: confidence interval.

5. Safety

5.1. PD-1/PD-L1 inhibitors related to hyperprogression of hepatocellular carcinoma

Most studies mentioned above have concluded that TACE, in combination with immunotherapy, can effectively control tumor progression and prolong the survival time of patients. However, complications accompanied by immunotherapy should also be paid attention. Hyperprogression, also known as hyper-progressive disease, is a flare-up of tumor growth upon ICIs [67]. Studies have reported that PD-1/PD-L1 inhibitors might fail to achieve an ideal effect due to hyperprogression among patients with different cancer types [68–70]. Hyperprogression is an unexpected response pattern observed in patients treated with ICIs. However, the incidence, mechanism, and impact of hyperprogression after PD-1/PD-L1 inhibitors treatment are not entirely known.

Some hypotheses have been established to clarify the mechanism of the hyperprogression of cancer. Viehl CT et al. found that reducing T regulatory cells could enhance the effect of antitumor drugs in mice models [71], and ICIs may activate T regulatory cells [72]. As the most commonly used immunotherapy in HCC, in some cases, the therapeutic effect of PD-1/PD-L1 inhibitors may be unsatisfactory due to the aggregation and immunosuppression of T regulatory cells. Besides, immune system dysfunction is primarily observed in patients with chronic liver disease and HCC [73]; thus, the impact of immune system dysfunction should also be considered.

Moreover, studies reported that ICIs might lead to the enhancement of immune function and the release of inflammatory factors. Inflammatory factors, such as leukocyte infiltration, inflammatory factor release, and angiogenesis, promote tumor progression and spread to the body's other organs [74].

Kato S et al. [75] found that patients with MDM2 family (MDM2 amplification can be found in about 7% of cancers) amplification or EGFR aberrations had poor clinical outcomes and significantly increased the rate of tumor growth after PD-1/PD-L1 inhibitors. Besides, the authors also suggested that genomic testing is required to verify if the cancer-specific alterations are associated with hyperprogression. Besides, PD-1/PD-L1 inhibitors may activate pathways, such as PI3K/AKT, WNT/β-catenin, and Mek/Erk MAP, which may promote the proliferation and invasion of tumor cells via complicated mechanisms [76,77].

Overall, the use of PD-1/PD-L1 inhibitors should be carefully evaluated because adverse effects related to immunotherapy are crucial in clinical practice. Although cancer hyperprogression is not common, the prognosis of patients with hyperprogression is very poor. It is necessary for clinicians to consider hyperprogression as a severe event, evaluate the efficacy of immunotherapy, perform clinical studies on hyperprogression in immunotherapy of cancers, and clarify the mechanism of hyperprogression in order to reduce the incidence of hyperprogression and improve the prognosis of patients with HCC.

5.2. Other adverse effects

Among the reported studies, most adverse events (AEs) were evaluated and found to be mild and tolerable, and no fatal AEs were reported in all the included studies. However, in some included studies, grade ≥3 AEs were tolerable, such as increased aspartate aminotransferase, lipase, and amylase; diarrhea; hypothyroidism; pneumonitis; and hyperthyroidism. Aes can be controlled by symptomatic treatment or reduction in drug dose or discontinuation.

Additionally, Robin Kate Kelley et al. [78] reported that the incidence of adverse events could be associated with the drug dose. However, the relationship between AEs and drug dose incidence is not a simple linear relationship. Overall, detailed long-term safety data were not reported among included studies because all included studies were published from 2020 to 2022, as safety issues should be investigated in detail.

6. Outlook and conclusion

The tumor immune microenvironment is exceedingly complex. The liver is an immunomodulatory organ with many innate and adaptive immune cells, which may lead to uncertain efficacy and AEs of PD-1/PD-L1 utilization [79,80].

For instance, studies have identified that in preclinical models of nonalcoholic steatohepatitis-induced HCC, PD-1 expanded activated $CD8^{+}PD1^{+}$ T cells within tumors but did not lead to tumor regression, indicates that tumor immune surveillance was impaired [81]. Besides, a

Table 3
Summary of ongoing clinical studies.

Registration No.	Status	Phase	Design	ICIs	Target	Combination therapy	First Posted	Lase-update posted	Estimated completion date	Detail
NCT04268888	Recruiting	Phase 2/3	522, 1:1 Parallel	Nivolumab	PD-1	TACE/TAE		July 16, 2020	June 2025	Dose of 480 mg IV.
NCT03572582	Active, not recruiting	Phase 2	49. Single-group Arm	Nivolumab	PD-1	TACE	June 28, 2018	September 8, 2021	June 2023	Initiated on day 2–3 after the first TACE. every two weeks (240 mg fixed dose IV)
NCT03143270	Recruiting	Early Phase 1	14, non-randomized parallel	Nivolumab	PD-1	DEB-TACE	May 8, 2017	July 6, 2022	April 2024	240 mg IV q 12 weeks for up to one year. In cohort 1, participants will begin nivolumab two weeks (± 5 days) after deb-TACE every two weeks. In cohort 2, participants will begin nivolumab every 2 weeks for 1 year and undergo deb-TACE 4 weeks after the initiation of nivolumab (± 5 day). Nivolumab will not be dosed on the day of embolization in this cohort. In cohort 3, nivolumab will be dosed every two weeks starting 4 weeks (± 5 days) prior to deb-TACE and continue every 2 weeks for up to one year. Nivolumab will be dosed on the day of embolization in this cohort. It will be administered before the deb-TACE procedure.
NCT03397654	Recruiting	Phase 1/2	26 participants, single group	Pembrolizumab	PD-1	TACE	January 12, 2018	February 15, 2021	December 31, 2021	NA
NCT04246177	Recruiting	Phase 3	950 participants, parallel, double-blinded	Pembrolizumab/Lenvatinib	PD-1/ VEGFR	TACE	January 29, 2020	July 18, 2022	December 31, 2029	Lenvatinib will be administered at a dose of 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) orally once a day during each 21-day cycle until progressive disease or unacceptable toxicity (up to 2 years [~35 cycles] or longer with Sponsor approval). Pembrolizumab will be administered via IV infusion at a dose of 400 mg once every 6 weeks (Q6W) for up to 2 years (~17 doses). Participants will undergo TACE as a background procedure of chemotherapeutic and embolic agent(s).
NCT03778957	Active, not recruiting	Phase 3	724 participants, parallel	Durvalumab	PD-L1	TACE	December 19, 2018	June 8, 2022	August 19, 2024	Arm A: TACE combination with Durvalumab Arm B: TACE combination with Durvalumab and Bevacizumab Arm C: TACE combination with Placebos
NCT03778957	Active, not recruiting	Phase 3	724 participants, parallel	Durvalumab + Bevacizumab	PD-1/ VEGFR	TACE	December 19, 2018	June 8, 2022	August 19, 2024	Arm A: TACE combination with Durvalumab Arm B: TACE combination with Durvalumab and Bevacizumab Arm C: TACE combination with Placebos
NCT03099564	Active, not recruiting	Early Phase 1	30, Single-group arm, open label	Pembrolizumab	PD-L1	Y90-TACE	April 4, 2017	March 23, 2022	July 2022	Pembrolizumab 200 mg IV every 3 weeks in conjunction with Y90 radioembolization (performed one week after the first dose of pembrolizumab)
NCT04174781	Active, not recruiting	Phase 2	61 participants, a phase II single-arm, open-label Study	Sintilimab	PD-1	DEB-TACE	November 22, 2019	June 9, 2022	December 30, 2022	Sintilimab was continued for a maximum of 3 cycles until surgical resection, radiologic disease progression, unacceptable toxicity, or withdrawal from the study, whichever occurred first.
NCT03638141	Recruiting	Phase 2	30 patients, a non-randomized parallel study	Durvalumab and Tremelimumab	PD-L1	DEB-TACE	August 20, 2018	October 10, 2022	November 2023	Starting at week 2, after initial DEB-TACE treatment, patients will receive Durvalumab in combination with tremelimumab as specified per protocol. Treatment will continue for up to 12 months, while receiving DEB-TACE. Repeat DEB-TACE will be provided Q8W if there is residual tumor that can be targeted.

(*continued on next page*)

Table 3 (*continued*)

Registration No.	Status	Phase	Design	ICIs	Target	Combination therapy	First Posted	Lase-update posted	Estimated completion date	Detail
NCT03778957	Active, not recruiting	Phase 3	724 participants, a randomized, double-blind, placebo-controlled, multicenter study	durvalumab	PD-L1	TACE	December 19, 2018	September 15, 2022	August 19, 2024	TACE in combination with Durvalumab/TACE in combination with Durvalumab and Bevacizumab/ TACE in combination with Placebos
NCT03937830	Recruiting	Phase 2	39 participants, a non-randomize study	Durvalumab	PD-L1	TACE	March 10, 2021		December 31, 2023	Durvalumab, bevacizumab, tremelimumab and TACE

TACE: transarterial chemoembolization; PD-1: programmed death 1; NA: not available; DEB-TACE: drug-eluting beads transarterial chemoembolization; VEGFR: vascular endothelial growth factor receptor; PD-L1: programmed cell death protein ligand.

meta-analysis of phase III clinical trials revealed that HCC revealed that immune therapy did not improve OS in patients with non-viral HCC [81]. The immune microenvironment of HCC is also related to the immune suppressive effect and progression; therefore, investigating the immune microenvironment of HCC is urgent for clinicians and scientists.

Overall, TACE, in combination with PD-1/PD-L1 immunotherapy, could reach a good survival time in most patients with HCC. However, when immunotherapy is administered, intratumoral and intertumoral heterogeneity in HCC should be considered. Besides, hyperprogression is a severe event that should be taken seriously, and the mechanism needs to be explored. Although more than the number of existing studies on PD-1/PD-L1 immunotherapy in combination with TACE is needed to conclude, many registered studies still need to be investigated, and we are looking to see those studies to add to the current clinical evidence. In addition, cytokine-induced killers and other immunotherapies also showed exciting results in treating cancer. Moreover, *in vitro* and *in vivo* studies are being performed; therefore, immunotherapy has many promising perspectives awaiting exploration.

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Author contributions

Jingxin Yan, Manjun Deng, Yutong Zhuang, Lushun Zhang, Haining Fan, and Yingxing Guo designed the review, performed the primary literature search, and extracted the data. Jingxin Yan, Manjun Deng, Shunyu Kong, Zhenwu Lei, Huangwei Wang, Ting Li, Haining Fan, and Yingxing Guo analyzed the data, all authors wrote the manuscript, and Jingxin Yan and Haining Fan were Journal Pre-proof responsible for revising the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethics statement

Ethics approvals were waived for this study because no patients' data were reported.

Informed consent

Informed consent was waived for this study because no patients' data were reported.

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