Liver Cancer

Editorial

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A Changing Role of Transarterial Chemoembolization in the Era of Immune Checkpoint Inhibitor plus Anti-VEGF/TKI plus Transarterial Chemoembolization: From Total Embolization to Partial Embolization (Immune Boost Transarterial Chemoembolization)

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Keywords
Hepatocellular carcinoma · Transarterial chemoembolization · Immune checkpoint inhibitor · Anti-VEGF · Tyrosine kinase inhibitor

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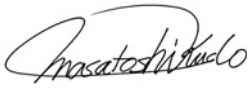

Editor *Liver Cancer*

Introduction

Transarterial chemoembolization (TACE) is the standard of care for intermediate-stage hepatocellular carcinoma (HCC). However, since the introduction of sorafenib in 2007, several treatments including lenvatinib [1], atezolizumab plus bevacizumab [2], durvalumab plus tremelimumab [3], and durvalumab alone [3] have been approved as first-line agents for unresectable HCC, and the combination of systemic therapy and TACE has been tested in intermediate-stage HCC. Regimens based on lenvatinib and atezolizumab plus bevacizumab have an extremely high response rate. Because the combination of systemic therapy with TACE frequently leads to complete response (CR), this treatment is actively used [4–8]. The results of the phase 3 EMERALD-1 trial showed that durvalumab plus bevacizumab plus TACE prolongs progression-free survival (PFS) better than TACE alone [9]. Ongoing trials such as the phase 3 LEAP-012 and EMERALD-3 trials are testing the effects of combination

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therapy with immune checkpoint inhibitors (ICIs), lenvatinib, and TACE [10]; the IMPACT trial combining atezolizumab plus bevacizumab with on-demand TACE [11] and the TALENTACE trial [12] are also ongoing. Positive results regarding the efficacy and safety of ICIs plus anti-VEGF/TKI plus TACE are highly expected [10].

When TACE was the only available treatment, one procedure that was commonly performed was "total embolization," in which all intrahepatic lesions are subjected to TACE to maximize the CR rate. Recently, however, treatment strategies have shifted from TACE with the aim of achieving CR in all nodules to "partial embolization" which is limited to 1–3 targets among multiple lesions to achieve volume reduction and provide an immune boost while preserving liver function [8, 11]. "Partial embolization" prevents liver function deterioration caused by total embolization and achieves CR in target lesions through a synergistic effect with ICIs plus anti-VEGF or tyrosine kinase inhibitors (TKIs) plus TACE. Therefore, "partial embolization" enhances the antitumor effect of ICI plus anti-VEGF/TKI therapy via the release of tumor antigens induced by TACE while achieving a partial response in intrahepatic lesions as a whole [8, 11]. In that sense, there has been a drastic shift in the role of TACE in the so-called "synergistic effect" of triple therapy (Fig. 1). In this Editorial, the shift in the role of TACE from total embolization to immune boost TACE is discussed.

A Changing Role of TACE after the Establishment of the Concept of TACE Failure/Refractoriness

The concept of TACE failure/refractoriness was defined by a joint consensus statement of the Japan Society of Hepatology (JSH) and the Japan Association of Liver Cancer (JLCA) (formerly Liver Cancer Study Group of Japan) [13–15]. This criterion for TACE failure was used in two retrospective studies that compared overall survival (OS) after TACE failure between two groups: patients who continued TACE and those who switched to sorafenib after TACE failure [16, 17]. The results showed that switching to sorafenib after TACE failure prolongs OS. The conclusion of these two studies was validated in the OPTIMIS study, a global non-interventional prospective, multicenter study [18]. Repeated TACE with "total embolization" also decreased the ALBI score, highlighting the negative impact of TACE on liver function [19]. Although TACE is a powerful therapeutic technique that physically destroys cancer cells, repeated "total embolization" decreases liver function and ultimately worsens OS. Because effective immunotherapy regimens and anti-VEGF or TKI therapies are now available, prompt transition to systemic therapy after TACE failure is a globally accepted concept.

A Changing Role of TACE after the Establishment of the Concept of TACE Unsuitability

Recently, the concept of TACE unsuitability was proposed by the Asian Pacific Primary Liver Cancer Expert (APPLE) Association [20] and the JSH [21]. Patients who meet these criteria, i.e., tumor burden exceeding the up-to-seven criteria or tumor gross types of diffuse, multinodular confluent type, simple nodular type with extranodular growth, or poorly differentiated HCC, are considered unsuitable for TACE. TACE has limited efficacy in these tumor types and is not recommended as initial therapy. Even in such TACE-unsuitable populations, prior administration of anti-VEGF agents such as lenvatinib or bevacizumab can normalize the abnormal tumor vasculature [22, 23]. This positive effect is mediated by the properties of VEGF inhibitors, which (1) decrease microvessel density, (2) decrease tumor interstitial pressure, (3) reduce the vascular permeability of the tumor, and thereby (4) improve drug delivery [22, 23](Fig. 1). It has become clear in recent years that upfront anti-VEGF agents can maximize the efficacy of TACE even in patients who were initially unsuitable for TACE.

Thus, it is essential to premedicate TACE-unsuitable cases with drugs that possess anti-VEGF activity, such as sorafenib, lenvatinib, and bevacizumab [5, 24]. Combining immunotherapy, anti-VEGF therapy, and TACE is a very effective approach for TACE-unsuitable HCC patients (Fig. 1). In the EMERALD-1 trial, the combination of ICIs plus the anti-VEGF agent with TACE prolonged PFS in both patients with tumor burden within and beyond the up-to-seven criteria [9]. The results of the phase 3 validation study demonstrating that durvalumab plus bevacizumab plus TACE is sufficiently effective even in patients with tumor burden exceeding the up-to-seven criteria are extremely important. In that sense, the EMERALD-1 trial is a practice-changing study.

A Changing Role of TACE in LEN-TACE Sequential Therapy

The beneficial effect of LEN-TACE sequential therapy on OS was first demonstrated in a 2019 proof-of-concept study that showed that LEN-TACE prolonged OS compared with TACE alone even in patients with a tumor burden exceeding the up-to-seven criteria (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.16–0.79; $p <$

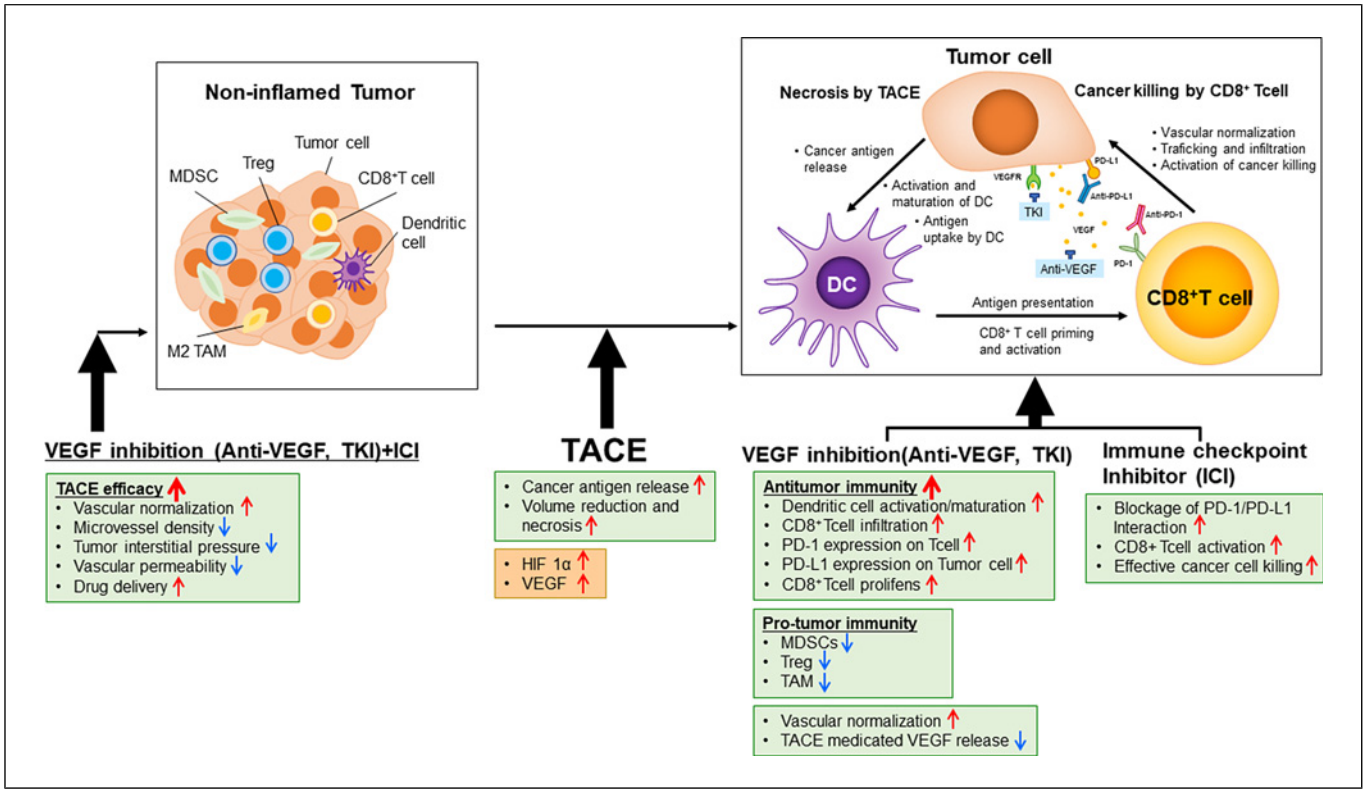
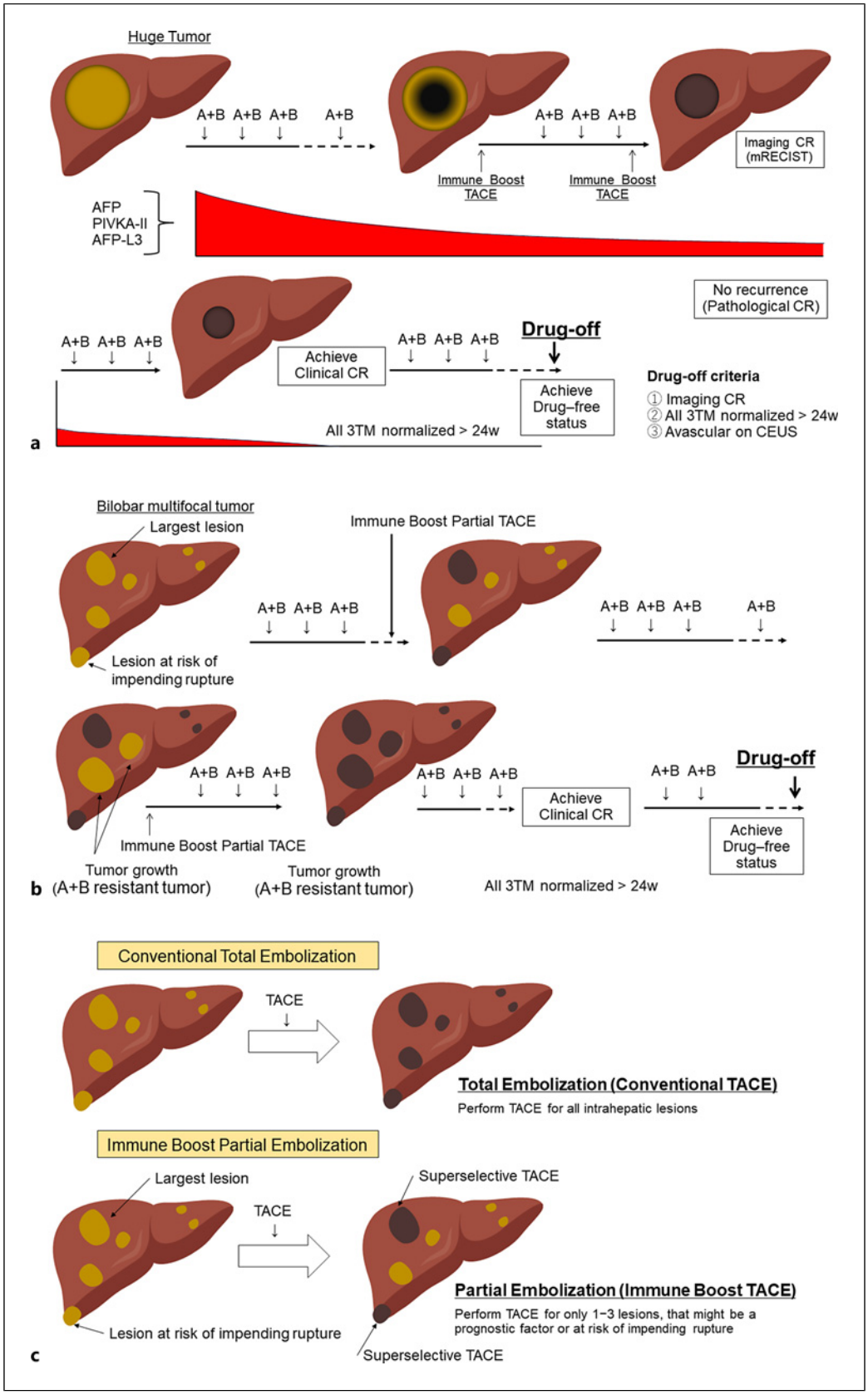


Fig. 1. Even in non-inflamed tumors and tumors that are not suitable for TACE, administration of anti-VEGF agents/tyrosine kinase inhibitors (TKIs) can normalize blood vessels and enhance the effect of TACE. The combined effect of TACE and immune checkpoint inhibitors (ICIs) also results in volume reduction and cancer antigen release. An unfavorable effect is that TACE-induced hypoxia upregulates VEGF, which suppresses the activation of CD8-positive T cells and increases the number of immunosuppressive cells such as Tregs, MDSCs, and TAMs. However, continued administration of anti-VEGF agents suppresses the increase in VEGF. In addition, tumor cells that have been destroyed by TACE release cancer antigens and lead to the activation and maturation of dendritic cells (DCs). The CD8-positive T cells recognize the tumor antigen and become activated CD8, causing residual intratumor infiltration and killing the immune-evaded tumor cells through the effects of ICIs. Therefore, ICI plus anti-VEGF/TKI plus TACE is considerably more effective than ICI plus anti-VEGF/TKI alone. Tregs, regulatory T cells; MDSCs, myeloid-derived suppressor cells; TAMs, tumor-associated macrophages.

0.01) [4]. Subsequently, the results of the TACTICS-L trial, which was almost identical in design to the TACTICS trial [24–26], demonstrated that the best response in the LEN-TACE group was an extremely high value of 67.7% [5]. The results of TACTICS-L showed a significantly prolonged PFS of 25.5 months and OS of 40.1 months [5].

Data from the TACTICS trial [24], which was the only positive trial of TACE and sorafenib combination therapy, were utilized to compare PFS and OS between LEN-TACE and TACE alone. The data of the TACE alone group ($n = 76$) extracted from the TACTICS trial [24] and the data of the LEN-TACE combination group ($n = 62$) extracted from the TACTICS-L trial were matched for baseline characteristics using the inverse probability waiting method, and PFS and OS were compared. PFS and OS were significantly better in the LEN-TACE group than in the TACE alone group (PFS: HR, 0.61; 95% CI, 0.39–0.95; $p = 0.033$; OS: HR, 0.68; 95% CI, 0.37–1.25).

A subanalysis performed after matching baseline characteristics using the inverse probability waiting method showed that the PFS HR was 0.70 for up-to-seven-in patients and 0.49 for up-to-seven-out patients. The OS HR was 0.89 for up-to-seven-in patients compared with 0.41 for up-to-seven-out patients, indicating that the combination of lenvatinib and TACE was more effective in the up-to-seven-out population. This result confirmed that TACE is unsuitable for patients with tumor burden exceeding up-to-seven criteria and that the combination of lenvatinib and TACE improves PFS and OS through a synergistic effect [5]. In this LEN-TACE



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regimen, patients were pretreated with lenvatinib 2–3 weeks before the first TACE, and instead of "total embolization" to achieve CR in all nodules, selective "partial embolization" was performed to preserve liver function as much as possible. Therefore, the liver function according to the ALBI score was also maintained [5].

A Changing Role of TACE in Atezolizumab plus Bevacizumab Followed by Curative Conversion Therapy (ABC Conversion)

In cases showing tumor shrinkage in response to atezolizumab plus bevacizumab, clinical CR, as defined by CR on imaging, normalization of all three tumor markers (AFP, PIVKA-II, and AFP-L3%), and disappearance of all intratumor blood flow determined by contrast-enhanced ultrasound [27], is frequently observed [8]. Even in patients with stable disease (SD), only the largest nodule was embolized using selective TACE, followed by subsequent atezolizumab plus bevacizumab. If the remaining tumor showed a tendency to enlarge, on-demand selective TACE (partial embolization) was performed on one or two nodules, followed by continuation of atezolizumab plus bevacizumab therapy with the aim of achieving clinical CR [8] (Fig. 2). Such ABC conversion therapy frequently results in pathological CR in tumors that shrink in size and become resectable [6–8] (Fig. 3).

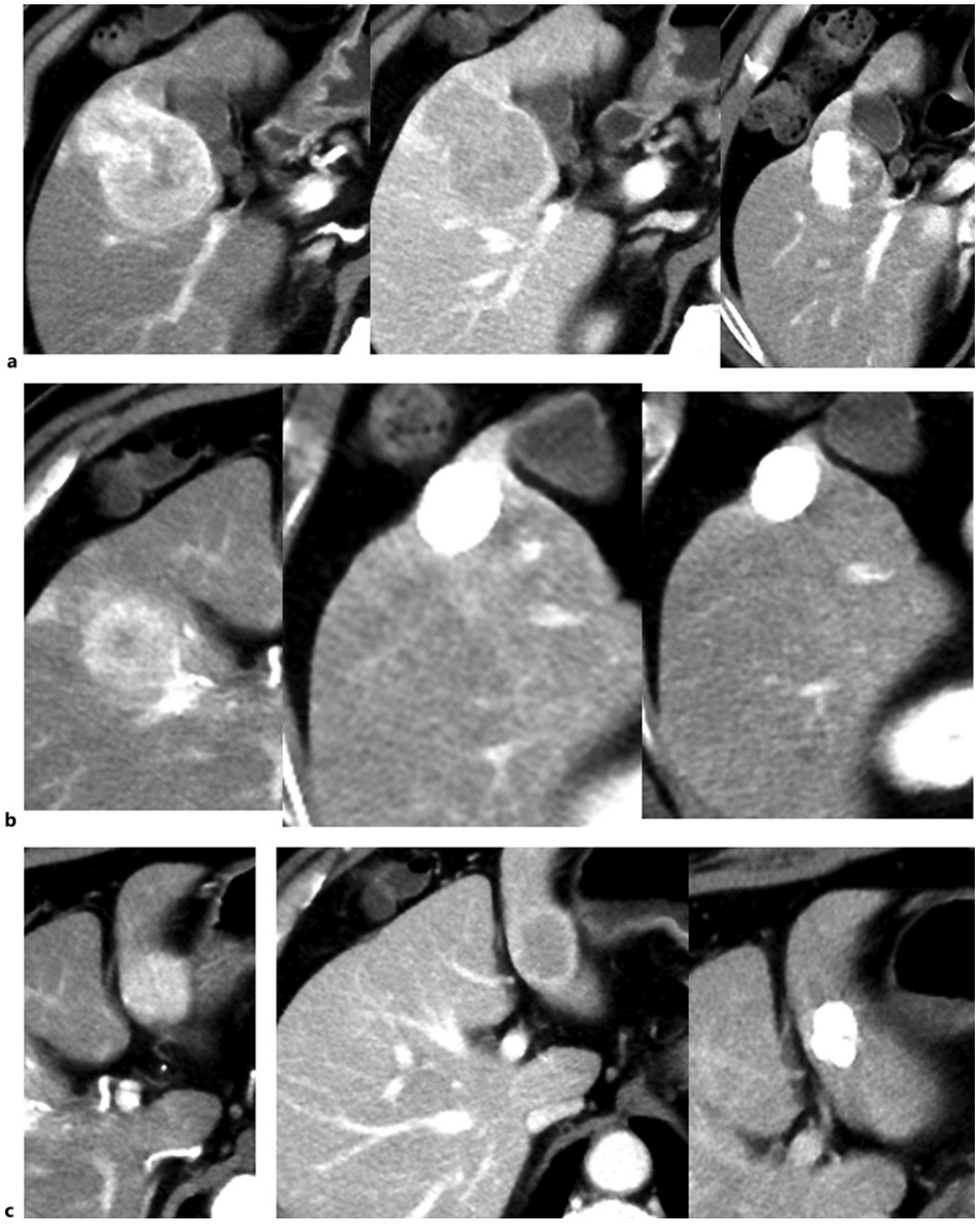
Although this proof-of-concept study was performed in patients with a high tumor burden and other TACE-unsuitable tumors such as diffuse-type HCC or poorly differentiated HCC, the clinical CR rate was 35%, and the drug-free rate was 23% [8], which is a highly favorable result. PFS and OS were extremely favorable in patients who achieved curative conversion compared with those who did not, and there were many cases of pathological CR in patients who underwent surgical resection with precise pathological examination [8] (Fig. 3).

When only TACE was available as a treatment option in intermediate-stage HCC, i.e., when no effective drugs for HCC were available before 2007, "total embolization" was commonly performed in all nodules to achieve radiological CR in a single TACE session. However, currently, the use of effective drugs with high response rates such as lenvatinib or immune-oncology (IO)-based systemic agents in combination with TACE may lead to marked changes in the role of TACE.

In cases in which CR can be achieved with a single TACE session, such as in patients with up-to-seven-in tumors, TACE can be performed on all nodules in a single session using super selective TACE, followed by atezolizumab plus bevacizumab therapy to lead to CR. In this patient subgroup, the role of TACE remains unchanged. However, in patients with TACE-unsuitable up-to-seven-out tumors, atezolizumab plus bevacizumab is the primary treatment, and TACE is not necessarily performed on all nodules but only on one to three among multiple nodules. Recent findings show that "partial embolization" induces antigen release and achieves volume reduction, ultimately resulting in a good prognosis (Fig. 1). This is because the antitumor effect of anti-PD-L1 can be enhanced through the infiltration of CD8-positive T cells into the tumor and the inhibition of immunosuppressive cells such as Tregs and myeloid-derived suppressor cells through the anti-VEGF effect (Fig. 1).

Because TACE also functions as an immune booster, performing "total embolization" of all intrahepatic nodules in one TACE session in cases of multiple nodules

Fig. 2. a In large tumors, after several cycles of atezolizumab plus bevacizumab (A + B), immune boost TACE is performed to treat residual tumor cells present at the tumor margin when intratumoral necrosis is achieved. Cycles of A + B therapy are administered to increase the necrotic effect in the remaining tumor and to achieve imaging complete response (CR). Continued A + B therapy after immune boost TACE results in normalization of all three tumor markers and clinical CR. Thereafter, drug-free status can be achieved by administering A + B until the drug-off criteria are met. A + B, atezolizumab plus bevacizumab; TACE, transarterial chemoembolization; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; AFP-L3, lens culinaris agglutinin-reactive fraction of AFP; CR, complete response; TM, tumor marker. **b** In bilobar multifocal tumors, atezolizumab plus bevacizumab followed by immune boost TACE is performed for the largest nodule only or for a nodule on the liver surface only that is about to rupture. Atezolizumab plus bevacizumab is continued, and if a tumor resistant to atezolizumab plus bevacizumab emerges, immune boost TACE is performed on the tumor and atezolizumab plus bevacizumab is continued. In some cases, clinical CR can be achieved by performing immune boost TACE and continuing atezolizumab plus bevacizumab for the tumor. Even non-treated nodules by TACE sometimes achieve CR by abscopal effect. Clinical CR and normalization of three tumor markers for at least 24 weeks are required to achieve drug-free status. **c** Conventional TACE is generally performed by total embolization, in which TACE is performed on all the tumors present in the liver to achieve CR in all nodules. However, this method can lead to liver function deterioration and ultimately poor survival. Immune boost partial embolization, on the other hand, aims to achieve an immunostimulatory effect by performing TACE on large or nearly ruptured tumors, thereby inducing the release of tumor antigens and activating the cancer immunity cycle.



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or for one large tumor is unnecessary. Instead, it is becoming more important to limit selective TACE to one to three significant nodules among multiple lesions to preserve liver function, followed by continuation of atezolizumab plus bevacizumab to ultimately lead to CR (Fig. 1, 2).

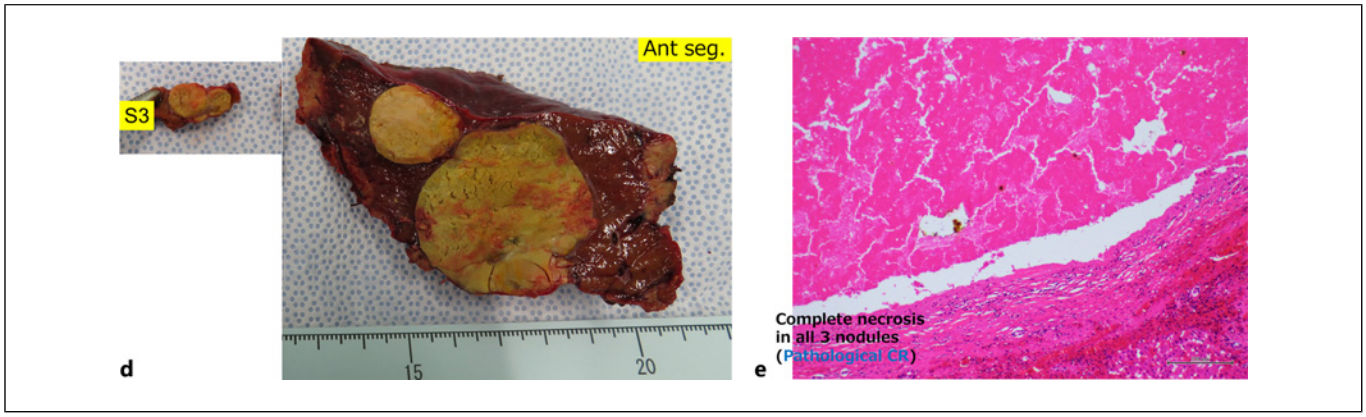

Fig. 3. A case of ICI plus anti-VEGF plus TACE achieving pathological CR. **a** Atezolizumab plus bevacizumab treatment of a typical HCC with enhancement in the arterial phase (left panel) and washout in the late phase (middle panel). After the introduction of atezolizumab plus bevacizumab, selective TACE was performed, but lipiodol accumulation was observed only at about 50% in S4 nodules. **b** A tumor in segment 5 showed enhancement in the arterial phase (left panel) and washout in the portal phase, and TACE was very effective in this tumor (middle panel). Subsequently, more tumor shrinkage was obtained (right panel). **c** A hypervascular lesion (left panel) with late washout (middle panel) detected in segment 2 was successfully treated with TACE (right panel). **d** Atezolizumab plus bevacizumab was then used to reduce the size of the tumor by killing the residual cancer cells, and a laparoscopic resection was performed. **e** Microscopic, pathological examination showed complete tumor necrosis (pathological CR) in all three nodules.

In summary, in patients with a high tumor burden, the role of TACE is not "total embolization" but "partial embolization" and "activation of the cancer immunity cycle," which enables the preservation of liver function (Fig. 2). The possible target nodules for selective TACE are as follows: (1) the largest nodule, (2) nodules on the liver surface that are at risk of rupture, or (3) nodules for which atezolizumab plus bevacizumab has limited effect (IO-resistant tumor) (Fig. 2b).

A Changing Role of TACE in the Era of IO-Based Triple Therapy (ICI plus anti-VEGF/TKI plus TACE/TARE)

The results of the EMERALD-1 trial presented at ASCO-GI in January 2024 showed the prolonged PFS benefit of durvalumab plus bevacizumab plus TACE versus TACE alone [9]. Several phase 3 clinical trials of IO-based triple therapy are ongoing. Among them, in the LEAP-012 trial design (pembrolizumab plus lenvatinib plus TACE vs. TACE alone), upfront lenvatinib 2–4 weeks before the first TACE will undoubtedly show good results in intermediate-stage HCC [10, 28]. The EMERALD-3 trial also compared the combination of durvalumab plus tremelimumab plus lenvatinib plus TACE with TACE alone using a design in which lenvatinib was started 1 week before the first TACE session [10]. Both trials showed an effective design similar to that of the TACTICS-L trial, which was based on the pre-administration of lenvatinib before the first TACE. The IMPACT trial was another randomized, controlled trial comparing atezolizumab plus bevacizumab plus on-demand TACE (immune boost partial TACE) versus atezolizumab plus bevacizumab alone in patients with SD [10, 11]. On-demand TACE is expected to physically destroy cancer cells and activate the cancer immunity cycle by inducing the release of cancer antigens [10, 11]. Specifically, in the intrahepatic control TACE arm, patients with SD after four cycles of prior atezolizumab plus bevacizumab are treated with on-demand super selective TACE targeting 1–3 of multiple nodules to prolong OS (Fig. 2b, c). In clinical practice, "partial embolization" performed in the middle of atezolizumab and bevacizumab treatment sometimes results in the disappearance of non-embolized nodules (the so-called "abscopal effect"). It is important to note that this trial was also designed to be preceded by bevacizumab, an anti-VEGF antibody. The protocol clearly states that the most crucial point is to avoid "total embolization," in which TACE is performed on all intrahepatic lesions, and to perform immune boost "partial embolization" in cases with a high tumor burden [11]. Immune boost "partial embolization" is fundamental in cases receiving the combination of ICIs plus anti-VEGF with locoregional therapy (Fig. 1, 2). Transarterial radioembolization instead of TACE is another immune boost locoregional therapy option.

Conclusion

Atezolizumab plus bevacizumab plus TACE is a routine strategy in clinical practice for achieving clinical and pathological CR (ABC conversion and ABC-TACE sandwich therapies) [6–8]. In this context, the combination of TACE with IO-based systemic therapy to achieve CR using several sessions of immune boost "partial embolization" rather than "total embolization" in a single session is becoming extremely important (Fig. 2b). The role of TACE, which in the past was aimed at achieving CR by performing "total embolization" on all intrahepatic nodules, is drastically changing into one in which the objective is to provide immune boost "partial embolization" to enhance the effect of IO-based systemic therapy and preserve liver function, eventually resulting in achieving pathological CR and/or improving survival [8, 10] (Fig. 1–3).

Statement of Ethics

No statement is needed because this study was based exclusively on published data.

Conflict of Interest Statement

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Author Contributions

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

Data Availability Statement

Data are not applicable because this is not a research article.

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