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Transarterial chemoembolization for renal cell carcinoma patients with liver metastases in the era of immunotherapy: A case series

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ABSTRACT

Treatment for renal cell carcinoma (RCC) has changed rapidly in the past decade with the widespread implementation of immune checkpoint inhibitors (ICIs) as first-line therapy in metastatic disease. The presence of liver metastases is a poor prognostic indicator but also has the potential to be a target for localized therapy. However, there is limited knowledge on the dynamics and long-term effects of combining liver-directed transarterial chemoembolization (TACE) with ICI therapy. We identified four patients with metastatic RCC (mRCC) and liver metastases who were treated concurrently with ICIs and TACE to metastatic liver lesions from our institutional database. We assessed treatment radiological responses and toxicity in this cohort. Liver-directed TACE with concurrent ICI was associated with radiological response or stabilization in all the liver lesions in the four patients in this cohort with a median time to locoregional liver metastasis progression-free survival of 8.3 months (range 6.0–11.1). The concurrent administration of ICI therapy and TACE to liver lesions was well tolerated with no new safety signals and no immune-related toxicities. Combining TACE with ICI in patients with mRCC showed promising response with limited toxicity. Future studies are warranted to clarify treatment timing and validate benefits.

Keywords: Immune checkpoint inhibitors, Liver metastasis, Renal cell carcinoma, Therapeutic chemoembolization

INTRODUCTION

The treatment landscape for metastatic renal cell carcinoma (mRCC) has radically changed in the past decade as a result of our better understanding of disease biology and targetable pathways. The emergence of novel immunotherapy in the form of immune-checkpoint inhibitors (ICIs) has altered the treatment landscape of the disease.[1] Liver metastases are detected in around 8–20% of patients with mRCC and have been shown to portend a poor prognosis.[2]

Liver-directed therapy is a form of metastasis directed therapy that is considered in highly selective patients with liver-predominant disease. The forms of liver-directed therapy that have been mostly utilized in RCC include surgical resection, ablation, and radiotherapy. Transarterial chemoembolization (TACE) is a targeted regional treatment modality with evidence of efficacy in both primary and secondary malignant liver lesions.[3] Little has been reported about the efficacy of TACE in mRCC combined with current gold-standard treatment methods including ICIs.[4,5] Furthermore, recent studies in hepatocellular carcinoma (HCC) demonstrated that TACE could boost the immune-response through several mechanisms which could enhance the anti-tumor activity of immunotherapy.[6]

Herein, we review our institutional experience of combining ICI therapy plus liver metastases directed TACE, including assessing the efficacy and safety of the procedure in combination with ICI.

MATERIAL AND METHODS

TACE selection criteria were extrapolated from those for HCC. Single, percutaneously accessible lesions <3 cm whose location portents little risk for biliary stricture or vascular injury are considered for ablation. For multifocal disease, or lesions >3 cm TACE is preferred.

TACE technique was as previously described for HCC.[3] Under conscious sedation through right common femoral access, a Simmons I glide catheter (Terumo, Sommerset, NJ) was used to select the celiac axis and a diagnostic arteriogram was performed. The vascular supply to the identified tumor was super-selected using a microcatheter (Renegade high Flow, Marlborough, MA). Microcatheter location was as peripheral as possible while still perfusing the entire targeted tumor [Figure 1]. A 1:1 oil-drug emulsion was made by mixing 10 mL of lipiodol (Guerbet, Princeton, NJ) with 10 mL of 0.9% saline containing 50 mg of doxorubicin and 10 mg of mitomycin C. A variable volume of 100–300 micrometer embolization particles (Embospheres, Merit Medical, South Jordan, Utah) were then used to complete stasis. Modified RECIST was used as response criteria.[7]

CASE REPORTS

We assessed the locoregional liver metastasis progression-free survival (PFS) and toxicity of four patients who were receiving ICI-based therapy for mRCC and underwent liver-directed conventional TACE [Table 1]. All four patients

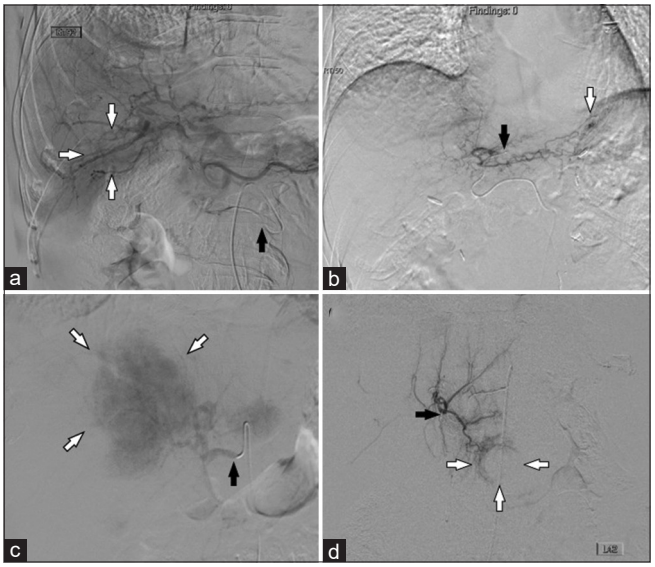

Figure 1: Four patients with RCC and liver metastasis treated with immunotherapy underwent TACE. Panels depict digital subtraction images from each angiographic procedure. White arrows demarcate tumors and black arrows mark the catheter tip. (a) A 65-year-old man with papillary RCC received TACE to his right liver lobe metastasis. (b) A 59-year-old female with clear cell RCC received TACE to her left liver lobe metastasis. (c) A 57-year-old male with *de novo* metastatic RCC received TACE to his large left liver lobe metastasis. (d) A 54-year-old female with metastatic MiTF/TFE translocation RCC received TACE to her left liver lobe metastasis. (RCC: Renal cell carcinoma, TACE: Transarterial chemoembolization.)

Table 1: Patient characteristics.

Patient	1	2	3	4
Sex	Male	Female	Male	Female
Age at diagnosis	66	51	56	54
Stage at diagnosis	I	II	IV	III
Age at recurrence	69	58	--	54
ECOG status at the time of TACE	0	0	0	2
Time from recurrence to detection of liver metastasis (months)	6	20	--	2
Prior Nephrectomy	Yes	Yes	No	Yes
Pathological Diagnosis	Papillary Type 2	Clear Cell Carcinoma	Clear Cell Carcinoma	MiT Family Translocation Carcinoma Phenotype
Extrahepatic Metastasis Sites	Lung, Peritoneum	Pancreatic Invasion, Contralateral Kidney	Pancreatic Invasion	Lung, Spine
Immunotherapy Regimen	Pembrolizumab + Axitinib	Nivolumab + Axitinib	Ipilimumab + Nivolumab	Nivolumab + Cabozantinib
Time from detection of liver metastasis to TACE (months)	13.2	34.4	6.6	17.2
Number of TACE sessions	1	2	3	2
Time from first TACE session to liver progression (months)	11.1	8.9	6.0	7.4

TACE: Transarterial chemoembolization, ECOG: Eastern cooperative oncology group.

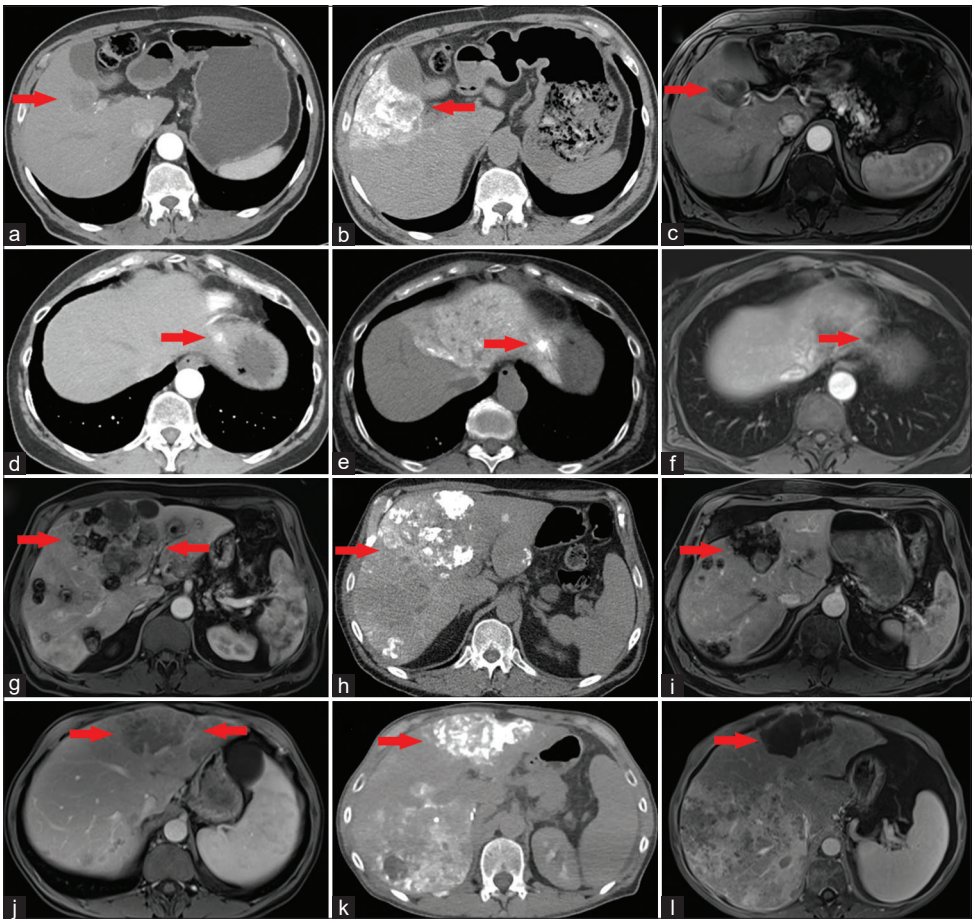

Figure 2: (a-c) A 65-year-old man with papillary RCC and liver metastasis was treated with TACE. (a) Abdominal CT scan before treatment, (b) CT scan at the time of treatment, and (c) contrast enhanced T1-weighted MRI 2-month post-treatment show the development of necrosis of the right lobe target lesion (red arrows). (d-f) A 59-year-old female with clear cell RCC and liver metastasis was treated with TACE. (d) Abdominal CT scan before treatment, (e) CT scan at the time of treatment, and (f) contrast enhanced T1-weighted MRI 1-month post-treatment show the development of complete necrosis of the left lobe targeted lesion (red arrows). (g-i) A 57-year-old male with *de novo* metastatic RCC including diffuse liver metastasis was treated with TACE. (g) Abdominal CT scan before treatment, (h) CT scan at the time of treatment, and (i) contrast-enhanced T1-weighted MRI 1-year post-treatment show significant reduction in the size of the large left lobe lesion with near complete necrosis of the residual portion (red arrows). (j-l) A 54-year-old female with metastatic MiTF/TFE translocation RCC and liver metastasis was treated with TACE. (j) Abdominal CT scan before treatment, (k) CT scan at the time of treatment, and (l) contrast enhanced T1-weighted MRI 6-month post-treatment show the development of complete necrosis of the large left lobe targeted lesion (red arrows). Red arrows point to corresponding tumor sites across time for each patient. (RCC: Renal cell carcinoma, TACE: Transarterial chemoembolization, CT: Computed tomography, MRI: Magnetic resonance imaging.)

had either liver disease stabilization or radiological response after undergoing TACE [Figure 2]. The procedure was well tolerated in all patients with minimal post-procedure abdominal pain and transient transaminitis without any immune-related toxicities. The median time to locoregional liver metastasis progression was 8.3 months (range 6.0–11.1) [Figure 3].

Patient 1

A 65-year-old male was diagnosed with papillary RCC of the left kidney and underwent a left partial nephrectomy. During surveillance, the patient was found to have recurrent metastatic disease in the lungs and in a right liver lobe lesion, biopsy confirmed metastatic papillary RCC. He started pembrolizumab plus axitinib with excellent disease response

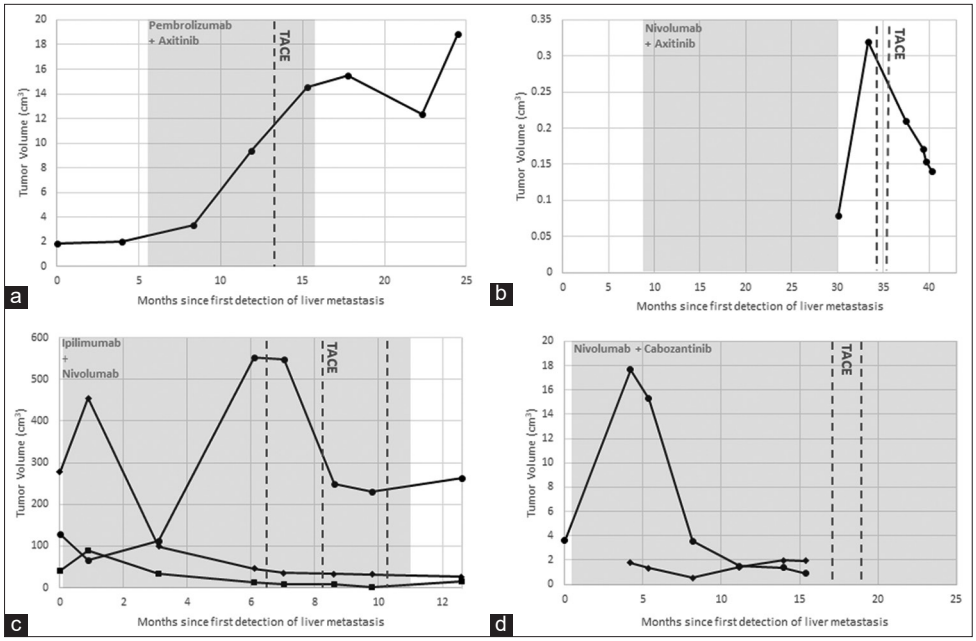

Figure 3: Four patients with RCC and liver metastases received immunotherapy and TACE treatment. (a-d) Immunotherapy regimens and select hepatic metastasis measurements are shown over time from first detection of liver metastasis to progression after TACE treatment. (a) Patient 1, a 65-year-old man with papillary RCC and liver metastasis was treated with TACE toward the end of his immunotherapy regimen which stalled growth of the target hepatic metastatic lesion. (b) Patient 2, a 59-year-old female with clear cell RCC and liver metastasis was treated with TACE after completing an immunotherapy regimen which caused a decrease in the size of a left hepatic metastasis. (c) Patient 3, a 57-year-old male with *de novo* metastatic RCC including diffuse liver metastasis was treated with TACE while on an immunotherapy regimen which led to a decrease in size of one hepatic mass and overall stability of his liver metastatic burden. (d) Patient 4, a 54-year-old female with metastatic MiTF/TFE translocation RCC and liver metastasis was treated with TACE while on an immunotherapy regimen which stabilized her liver metastatic burden. Measurements were taken from contrast enhanced CT scans. Dashed vertical lines represent dates of TACE sessions and shaded areas show the timing of immunotherapy treatment. (RCC: Renal cell carcinoma, TACE: Transarterial chemoembolization, CT: Computed tomography.)

including reduction of the lung nodules and stabilization of the right liver lobe lesion. Approximately 8 months after starting pembrolizumab and axitinib, he developed progression of the solitary right liver lobe lesion measuring 2.8 cm for which he underwent TACE. The lesion was stable for 11.1 months from the date of the TACE procedure. During this time period, the patient had disease progression in other locations which required changing systemic therapy. The TACE procedure was well tolerated with transient transaminitis which recovered within a few days.

Patient 2

A 59-year-old female was diagnosed with clear cell mRCC and started systemic therapy with nivolumab plus axitinib. After 24 months of systemic therapy, she developed new left lobe liver metastasis with numerous small unmeasurable right lobe lesions. She received two rounds of TACE, one to each lobe which led to significant disease response. Of note, she did experience pain, nausea, and one day of jaundice following one of her TACE sessions which resolved quickly but no immune-related toxicities were encountered. The liver metastasis PFS in this patient was 8.9 months with progression in the right liver lobe lesions after which the patient was switched to a new systemic therapy.

Patient 3

A 57-year-old male was diagnosed with *de novo* clear cell mRCC, including a left renal primary tumor, metastatic adenopathy, and diffuse hepatic metastases. He started systemic therapy with ipilimumab plus nivolumab which led to a heterogenous response of the liver lesions with growth of a dominant central metastasis but apparent regression and stabilization of others. He underwent three rounds of TACE, leading to a notable regression of the dominant liver lesion. The TACE procedure was well tolerated with no immune-related toxicity. The liver metastasis PFS in this patient was

6.0 months with the development of new liver lesions after which the patient switched to a new systemic therapy.

Patient 4

A 54-year-old female was diagnosed with MiTF/TFE translocation RCC (tRCC) with lung and liver metastatic lesions. She was started on nivolumab plus cabozantinib which was associated with disease response with resolution of the lung nodules and reduction in the liver lesions. She was maintained on systemic therapy given the rarity of tRCC and limited treatment options. However, 17 months after starting nivolumab plus cabozantinib, she had evidence of oligo-progressive liver disease for which she underwent two rounds of TACE, after which the majority of her liver lesions showed only post-treatment effects without growth. The liver metastasis PFS in this patient was 7.4 months.

DISCUSSION

We report four cases of mRCC treated with liver-directed conventional TACE along with immunotherapy-based regimens. All four patients had a significant reduction of liver metastatic burden. Our experience with concurrent liver-directed TACE and ICI therapy in RCC presents pilot data on the possible synergy and immunogenic effect between liver-directed TACE and ICI in RCC patients.

Conventional TACE works by arterial injections of lipiodol-based chemotherapy emulsions plus an embolizing agent targeted at vascularized tumor sites.[3] The result is localized tumor cell death with limited systemic toxicity. It has been hypothesized that cell death plays an important role in altering tumor immunity; thus, a synergistic interaction may exist between localized treatments and systemic immunotherapy. One study showed that TACE could unmask tumor antigens in HCC, increasing CD4+ T-cell response.[8] Recent studies have shown both the safety and efficacy of combining ICIs and TACE for HCC.[9] In addition, the anti-angiogenic properties of tyrosine kinase inhibitor (TKI) may also synergize with TACE.[10] Possible benefits need to be balanced with the potential to increase adverse events including bleeding and autoimmune hepatitis.

In 2018, based on the CheckMate 214 trial, ICIs ipilimumab and nivolumab were approved for patients with intermediate or poor risk mRCC. Standard of care before this was either targeted therapies for vascular endothelial growth factor (VEGF)/mammalian target of rapamycin (mTOR) or interleukin-2, which had replaced systemic chemotherapy. At our institution, the standard treatment for patients with mRCC is systemic therapy with ICI combinations, including nivolumab plus ipilimumab or ICI plus VEGF-TKI combinations. In patients with oligometastatic disease, locoregional therapy is preferred such as metastatectomy, radiotherapy, ablation, or TACE.

Prior studies have reported the use of TACE in RCC in combination with either systemic chemotherapy or targeted therapy. Nabil *et al*. reported a series of RCC patients treated with TACE from the early 2000s who had systemic chemotherapy, either mitomycin alone or in combination with gemcitabine.[4] Of the 22 patients, 13.7% had partial responses and 59% were reported as having subsequently stable disease. Pierro *et al*. reported on a larger cohort of GU cancer patients treated with liver-directed therapy from 2005 to 2016 including ten patients with RCC.[5] Systemic treatments included VEGF/mTOR inhibitors and interferon/interleukins. Median survival time after liver-directed therapy for the RCC cohort was 24 months (5–45 months). To date, no study has reported on TACE outcomes in RCC in combination with ICIs.

Our cases pose multiple questions to which future trials could be designed around. It will be important to pursue larger scale trials designed to validate the efficacy and safety of TACE for patients with liver mRCC undergoing immunotherapy. Another key question will be determining optimal timing for TACE during the course of a patient's immunotherapy treatment. Performing TACE earlier or even extending the timeline of immunotherapy to potentially enhance the effect of TACE could be considered.

CONCLUSION

We present four patients with RCC liver metastasis who achieved significant clinical benefit to liver metastases directed TACE concurrently with ICI. Our results are hypotheses generating on the potential synergy and immunogenic effect of combining TACE with ICI. Future clinical trials are warranted to explore the role of combing liver metastases directed TACE concurrently plus ICI in patients with RCC in a prospective setting.

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Ethical approval

The research/study approved by the Institutional Review Board at Johns Hopkins, number IRB00304265, dated March 25, 2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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