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Editorial Board Member of *World Journal of Clinical Cases*, Baharudin Ibrahim, BPharm, PhD, Associate Professor, Pharmacist, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur 50603, Malaysia. baharudin.ibrahim@um.edu.my

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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CASE REPORT

Successful multidisciplinary therapy for a patient with liver metastasis from ascending colon adenocarcinoma: A case report and review of literature

Xiao-Rong Tan, Juan Li, Hua-Wei Chen, Wei Luo, Nan Jiang, Zheng-Bo Wang, Shuai Wang

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Xiao-Rong Tan, Oncological Department of Oral and Maxillofacial Surgery, The First Affiliated Hospital of Xinjiang Medical University, School/Hospital of Stomatology Xinjiang Medical University, Urumqi 830054, Xinjiang Uygur Autonomous Region, China

Juan Li, Hua-Wei Chen, Wei Luo, Nan Jiang, Zheng-Bo Wang, Shuai Wang, Department of Oncology, Daping Hospital, Army Medical University, Chongqing 400042, China

Corresponding author: Shuai Wang, MS, Associate Chief Physician, Department of Oncology, Daping Hospital, Army Medical University, No. 10 Changjiang Branch Road, Yuzhong District, Chongqing 400042, China. sharondenise_mine@163.com

Abstract

BACKGROUND

Liver metastasis is the most common form of distant metastasis in colorectal cancer, and the only possible curative treatment for patients with colorectal liver metastases (CRLM) is hepatectomy. However, approximately 25% of patients with CRLM have indications for liver resection at the initial diagnosis. Strategies aimed at downstaging large or multifocal tumors to enable curative resection are appealing.

CASE SUMMARY

A 42-year-old man was diagnosed with ascending colon cancer and liver metastases. Due to the huge lesion size and compression of the right portal vein, the liver metastases were initially diagnosed as unresectable lesions. The patient was treated with preoperative transcatheter arterial chemoembolization (TACE) consisting of 5-fluorouracil/Leucovorin/oxaliplatin/Endostar®. After four courses, radical right-sided colectomy and ileum transverse colon anastomosis were performed. Postoperatively, the pathological analysis revealed moderately differentiated adenocarcinoma with necrosis and negative margins. Thereafter, S7/S8 partial hepatectomy was performed after two courses of neoadjuvant chemotherapy. Pathological examination of the resected specimen revealed a pathologically complete response (pCR). Intrahepatic recurrence was detected more than two months after the operation, and the patient was then treated with TACE consisting of irinotecan/Leucovorin/fluorouracil therapy plus Endostar®. Subsequently, the patient was treated with a γ-knife to enhance local control. Notably, a pCR was reached, and the patient's overall survival time was > 9 years.

CONCLUSION
Multidisciplinary treatment can promote the conversion of initially unresectable colorectal liver metastasis and facilitate complete pathological remission of liver lesions.

Key Words: Initially unresectable colorectal liver metastasis; Conversion chemotherapy; Multidisciplinary therapy; Pathological complete response; Transcatheter arterial chemoembolization; Case report

Core Tip: We report a multidisciplinary strategy, including 5-fluorouracil/Leucovorin/oxaliplatin/Endostar® (mFOLFOX6 plus Endostar®) and transcatheter arterial chemoembolization, that may help improve resectability of initially unresectable colorectal liver metastasis (CRLM) and achieve pathologically complete response (pCR). After the recurrence of liver metastasis, the patient received TACE comprising irinotecan/Leucovorin/fluorouracil therapy plus Endostar® and was treated with γ-knife. The patient's overall survival time exceeded 9 years. To date, this is the first case that mFOLFOX6 combined with Endostar® in conversion therapy of initially unresectable CRLM and liver metastases that achieved pCR. Our study implies that Endostar® has a potential value in conversion therapy and combination therapy of initially unresectable CRLM.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, ranking third in terms of incidence (9.7% of all cancer cases worldwide) and second in mortality (9.4% of all cancer mortality) globally[1]. Liver metastasis is the most common cause of death in CRC patients, and liver metastasis prevalence is approximately 15%-42% in this population[2,3]. The only possible curative treatment for patients with colorectal liver metastases (CRLM) is hepatectomy[4]. However, only about 25% of CRLM patients have indications for liver resection at the initial diagnosis[5]. For patients with irresectable CRLM, the standard care remains first-line systemic chemotherapy combined with antiangiogenic or targeted therapy to shrink tumors to allow patients to receive resection[6]. Multidisciplinary treatments, including regional hepatic intra-arterial chemotherapy[7], chemoembolization[8], stereotactic radiation therapy[9], targeted therapy[10], anti-angiogenic therapy[11], immunotherapy[12], and ablation procedures (radiofrequency ablation and microwave ablation)[13,14], improve the survival rate and prognosis of patients with CRLM[15,16]. Here, we report a case of conversion chemotherapy, including 5-fluorouracil/Leucovorin/oxaliplatin/Endostar® (mFOLFOX6 plus Endostar®) and transcatheter arterial chemoembolization (TACE), which promoted the successful conversion of initially unresectable CRLM into resectable CRLM with surgical indications and resulted in pathologically complete response (pCR).

CASE PRESENTATION

Chief complaints

A 42-year-old man presented to the hospital with pain in his right upper abdomen and anorexia in July 2013.

History of present illness

To date, there has been no evidence of disease progression, and the patient's overall survival (OS) time was > 9 years.

History of past illness

He had no previous history of hepatitis B or C, serious diseases, operations, or hospitalizations.

Personal and family history

The patient had no significant personal or family history.

Physical examination

Physical examination showed a temperature of 36.3 °C, a heart rate of 87 bpm, and a blood pressure of 15.7/9.2 kPa. There was no tenderness, rebound pain, or muscle tension in the abdomen. The upper boundary of the liver was located within the fourth intercostal space of the right midclavicular line, and the lower boundary of the liver was located approximately 2 cm below the costal margin. There were no other obvious abnormalities.

Laboratory examinations

Serum indicators were as follows: Carcinoembryonic antigen, 23.22 ng/mL (0-5 ng/mL), and aspartate aminotransferase, 115.6 U/L (15-40 U/L).

Imaging examinations

A colonoscopy revealed a moderately differentiated adenocarcinoma. The expression of *BRAF-V600E* and *RAS* was not determined. Enhanced computer tomography (CT) of the whole abdomen revealed ascending colon cancer (Figure 1A) with a single large low-density lesion in the liver (14.1 cm in length, Figure 1B). A CT scan of the chest, brain, and bone revealed no other abnormalities.

FINAL DIAGNOSIS

The patient was diagnosed with colon cancer and liver metastases. The clinical stage was T3N0M1a stage IVa (American Joint Committee on Cancer's Cancer Staging Manual 2010). Due to the huge liver metastatic lesions and compression of the right portal vein, the CRLM were initially diagnosed as unresectable lesions.

TREATMENT

The first multidisciplinary team discussion recommended the conversion therapy model of systemic chemotherapy combined with anti-angiogenesis therapy to strive for the opportunity of surgical resection. mFOLFOX6 has been used as a cornerstone in the combination chemotherapy treatment of CRC[17] and has been considered the first-line standard chemotherapy regimen for advanced CRC. Neutropenia is the most common adverse event of grade 3 or 4 after combination treatment with mFOLFOX6 and bevacizumab[17], and the high cost of bevacizumab continues to be a huge obstacle to its clinical use in China. Moreover, accumulating evidence suggests that the use of Endostar® does not significantly increase the level of chemotherapy toxicity[18] and tends to be accepted by many patients because of the relatively low economic burden. Moreover, studies have shown that Endostar® combined with chemotherapy can prolong progression-free survival and OS rates in patients with advanced CRC [11,19-22]. Hence, combined therapy including mFOLFOX6 plus Endostar® [day 1:5-fluorouracil (5-FU) 400 mg/m^2 (perfusion *via* arterial catheter); leucovorin (LV) 200 mg/(m^2·2 h) with oxaliplatin 85 mg/m^2 (perfusion *via* arterial catheter); Endostar® 3 mL (perfusion *via* arterial catheter), 5-FU 2400 mg/(m^2·44 h), and Endostar® 18 mL/(44 h) continuous infusion every 2 wk] was chosen as the conversion chemotherapy. After four courses, enhanced CT of the whole abdomen revealed that the low-density metastatic lesion in the liver had shrunk from 14.1 to 5.9 cm, although the tumor size in the ascending colon was not significantly reduced (6.8 to 5.4 cm) (Figure 1C and D). Therefore, radical right-sided colectomy and ileum transverse colon anastomosis were performed. Histological examination demonstrated moderately differentiated mutant kirsten rat sarcoma viral oncogene homolog adenocarcinoma with necrosis and negative margins. The cancer tissue invaded the whole layer of the intestinal wall and involved the nerve, and the formation of an intravascular tumor thrombus was observed. No lymph node metastasis was observed after surgery (0/13). The pathological response grade of the tumor after chemotherapy was grade 2 (Figure 2A).

Subsequently, the patient received another two cycles of TACE consisting of mFOLFOX6 plus Endostar® after radical resection of colon cancer. A whole abdominal CT scan revealed that the colon cancer surgery area was stable (Figure 1E), but the low-density metastatic lesion in the liver had shrunk from 5.9 to 5.2 cm (Figure 1F). As imaging examinations suggested that the liver lesions were further reduced, a second multidisciplinary team discussion was immediately performed. Resection of the hepatic metastasis was performed one month after the Endostar® was stopped. A pathological biopsy of the resected specimen revealed no cancerous cells in the liver metastases; necrosis was observed in most areas of the specimen. The pathological response grade of the tumor after chemotherapy was grade 0 (Figure 2B). The patient recovered promptly after both surgical procedures.

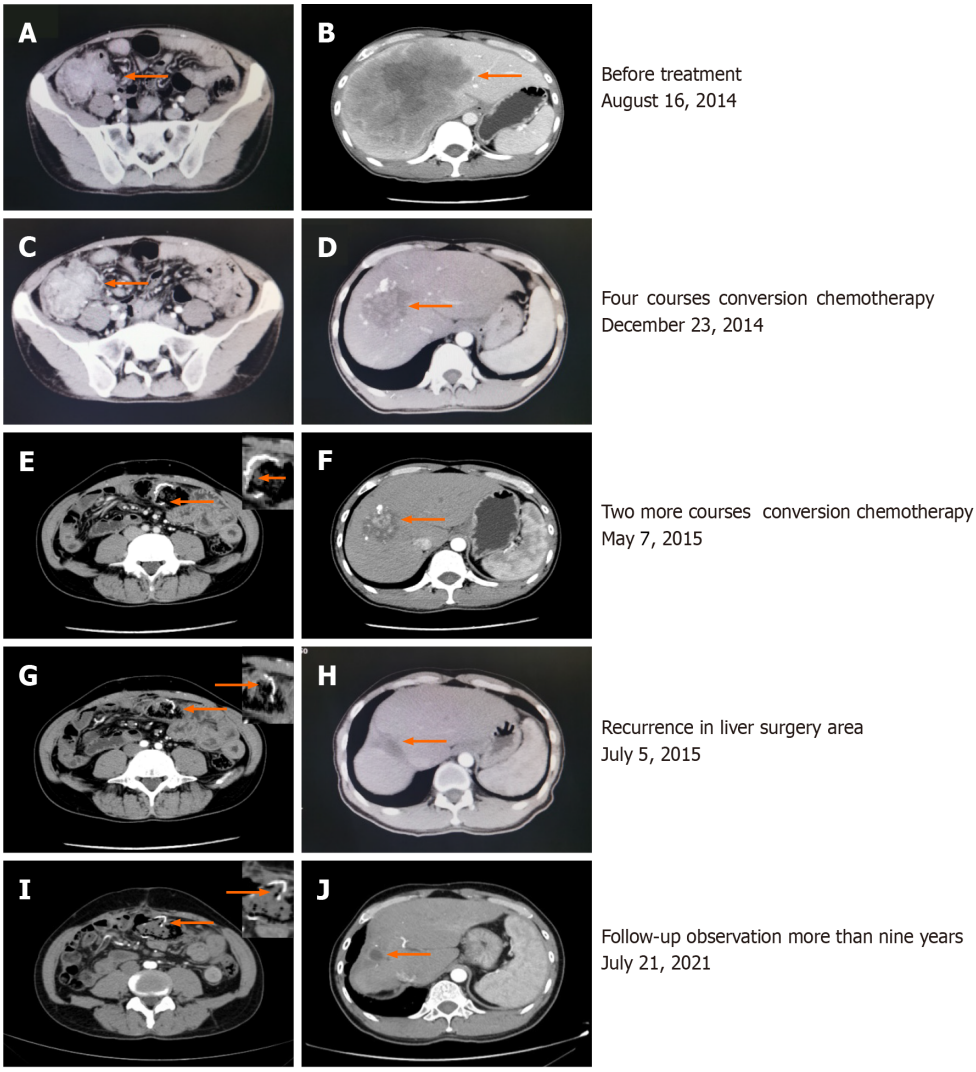

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Figure 1 Enhanced computed tomography. A: Malignant tumors in the ileocecal area and lymph nodes of varying sizes were observed adjacent to the mesangium, and metastasis was suspected; B: A huge liver metastasis in the right lobe of the liver, approximately 13.7 cm × 14.1 cm in size (arrow), with compression of the right portal vein; C and D: After four courses of treatment, the tumor in the ascending colon was not significantly reduced (6.8 to 5.4 cm), and the low-density metastatic lesion in the liver had shrunk from 14.1 to 5.9 cm; E, H, and I: The anastomosis in the colon cancer surgery area was unobstructed, and no abnormally enhanced lesions were seen; F: After another 2 cycles of conversion chemotherapy, the liver mass was significantly reduced to approximately 5.2 cm in size, with multiple lipiodol deposits on the edges; G: Residual liver parenchymal nodular enhancement in the right lobe of the liver (3.0 cm in length) that was considered a postoperative recurrence; J: A sheet-like low-density shadow was seen in the right lobe of the liver, with a size of approximately 1.6 cm × 1.5 cm, and no abnormal enhancement was observed.

Unfortunately, more than 2 mo after liver metastasis resection, the patient's serum carcinoembryonic antigen (CEA) level rose to 38 ng/mL, and a CT scan revealed a single low-density lesion in the liver surgery area (3.0 cm in length, Figure 1G). This was considered a postoperative recurrence. At the same time, the colon cancer surgery area remained stable (Figure 1H). Therefore, TACE consisting of 5-FU/LV/irinotecan and Endostar® (FOLFIRI plus Endostar®) was commenced. Studies have suggested that the γ-knife, a specific form of stereotactic radiotherapy, can avoid damaging the surrounding critical tissue for liver oligo metastases. Owing to the good local control effect and survival rates, γ-knife has become an effective option for patients with advanced CRC[23,24]. Therefore, the γ-knife was utilized to treat the recurrent liver lesions with a total dose of 35 Gray after two courses of TACE consisting of FOLFIRI plus Endostar®. The patient attended regular follow-up appointments for the analysis of serum CEA levels and an abdominal CT scan.

OUTCOME AND FOLLOW-UP

By the time of submission of this paper, there was no evidence of disease progression (Figure 1I and J), and the survival time had been more than 9 years. The timeline of the patient's treatment is shown in

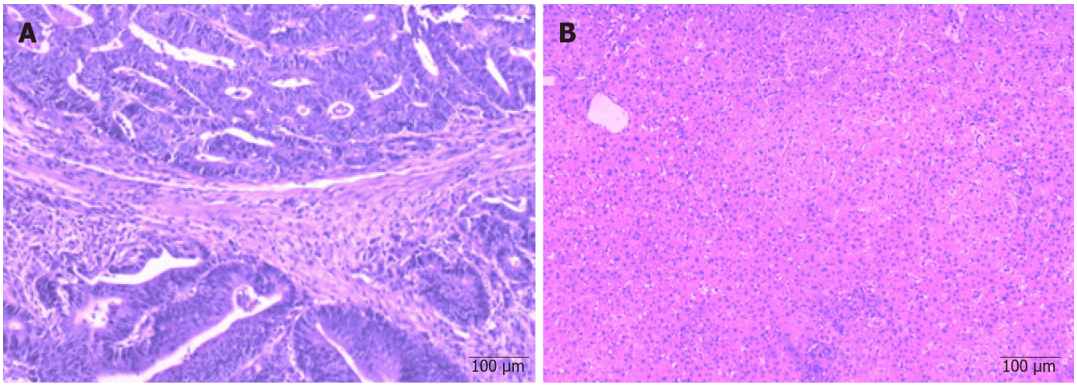

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Figure 2 Hematoxylin-eosin staining (× 100). A: The resected specimen (right colon) showed a massive moderately differentiated adenocarcinoma with necrosis. The cancer tissue invaded the entire intestinal wall and involved the nerves. Intratumoral vascular thrombosis was observed, and no cancer metastasis was seen in the peri-intestinal lymph nodes; B: The surgical resection specimen (right liver tumor) showed no cancerous cells in the liver metastasis, fibrous tissue hyperplasia, collagenous necrosis, and inflammatory cell infiltration, surrounding liver tissue congestion, hemorrhage, or inflammatory cell infiltration.

Figure 3.

DISCUSSION

Over 1.9 million new cases of CRC (including cancer of the anus) and 935000 CRC-related deaths were estimated to have occurred in 2020; approximately one in 10 cancer cases or deaths was related to CRC [1]. Currently, hepatic resection is the only possible radical treatment for patients with CRLM[4]. However, only about 25% of patients with CRLM have indications for liver resection at first diagnosis [5]. The most common metastatic site is the liver. For patients with unresectable CRLM, the standard care remains first-line systemic chemotherapy combined with antiangiogenic or targeted therapy to shrink tumors enough to allow for resection. mFOLFOX6 is commonly used as a cornerstone of combination therapy[17] and is considered the first-line standard treatment for advanced CRC. However, chemotherapy response rates are low, and severe dose-limiting toxicities can occur.

In 1971, researchers[25] proposed that the formation of new tumor blood vessels led to the growth and metastasis of cancer; thus, angiogenesis inhibitors, such as bevacizumab and Endostar®, have been developed for cancer treatment[26,27]. Endostar® and bevacizumab showed competitive anti-tumor efficacy. Bevacizumab is a recombinant human monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A)[28]. Endostar®, developed in China, is a recombinant human vascular endothelial inhibitor and multi-targeted tumor cell inhibitor. Endostar® directly inhibits the proliferation of vascular endothelial cells and exerts its anti-angiogenic effects through several targets, including VEGF, VEGF receptor-2 (VEGFR-2), and the platelet-derived growth factor receptor[29]. It can also normalize tumor blood vessels and exert anti-tumor effects[30]. The combination treatment of mFOLFOX6 with bevacizumab may lead to the most common grade 3 or 4 adverse events of neutropenia[17] and the high treatment cost of bevacizumab is still a huge obstacle to its clinical use in China. Endostatin is the strongest endogenous angiogenesis inhibitor of vascular endothelial growth factor expression and tumor angiogenesis[31]. Recombinant human endostatin, Endostar®, is a new recombinant human endostatin developed in China and has achieved good results in treating various advanced malignant tumors[21,22]. Notably, Endostar® has shown promise for the treatment of CRC[20,32]. Studies have demonstrated that combination therapy of FOLFOX with Endostar® can improve clinical efficacy and objective response rate and prolong PFS and OS rates[11, 19], and chemotherapy combined with Endostar® does not significantly increase chemotherapy toxicity [18] and is easier to be accepted given its relatively lower price. Therefore, combined therapy with mFOLFOX6 and Endostar® was chosen as neoadjuvant chemotherapy in this case.

Liver metastasis is the most common cause of death in CRC patients, and the prevalence of liver metastasis is approximately 15%-42% in this population[2,3]. With the continuous improvement of surgical methods, such as two-stage hepatectomy and TACE[14], more CRLM patients have the opportunity to undergo surgical treatment. Strategies aimed at downstaging large or multifocal tumors to enable curative resection are appealing. The decision of surgery for CRLM patients must consider many factors, including the order of liver surgery. TSH for CRLM is widely used and has satisfactory survival outcomes because it can reduce the huge surgical trauma caused by simultaneous operations [33]. While the 5-year survival rate after resection of CRLM is approximately 47% to 60%[34,35], 50% to 70% of patients still relapse after hepatectomy, and about one-third of them have isolated recurrence in

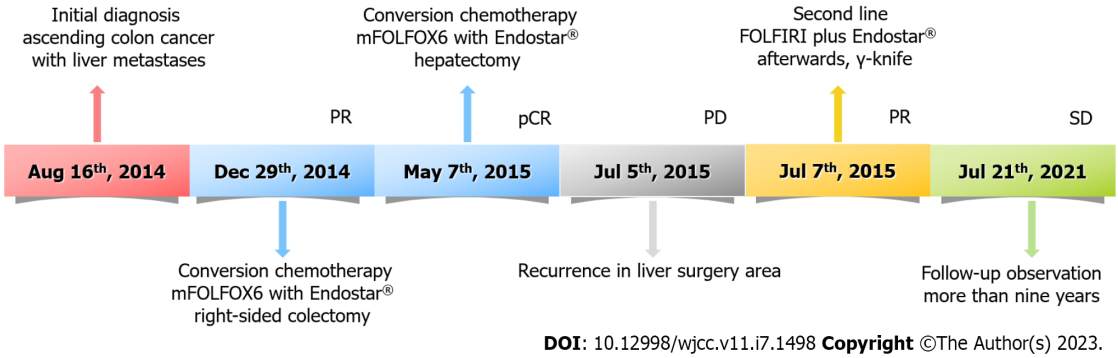

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Figure 3 The timeline of treatment. PR: Partial response; pCR: Pathologically complete response; PD: Progressive disease; SD: Stable disease; mFOLFOX6: 5-Fluorouracil/Leucovorin/oxaliplatin.

the liver[36].

Stereotactic radiation strategies have become an important treatment for unresectable CRLM. Therefore, stereotactic radiotherapy can be considered for the local control of liver metastases[23,37,38] and postoperative recurrence in the liver. The γ-knife, a specific form of stereotactic radiotherapy, can highly concentrate the target dose into a maximum focal spot and avoid damaging the surrounding critical tissue for liver oligometastases[24]. Thus, the γ-knife for liver metastasis is a safe and effective treatment that achieves high local control rates and enhanced survival rates among CRLM.

The groundbreaking progress in cancer immunotherapy in recent years has revolutionized the field of oncology with unprecedented survival rates in multiple cancer types[39]. Tumor escape and immune coordination are related to the recurrence of CRC, and major discoveries about the immune response in the recurrence of CRC have been made[40]. In the future, the combination therapy of mFOLFOX6 with immunotherapy will be chosen as the conversion treatment for CRLM. Unfortunately, this patient had not undergone next-generation sequencing to determine the status of immunotherapy markers in the past. Therefore, we could not determine the possibility of immunotherapy.

CONCLUSION

We report a case of initially unresectable advanced colon cancer with liver metastases that were successfully converted into resectable CRLM using multidisciplinary strategies, including mFOLFOX6+Endostar® and TACE. Surprisingly, a pCR to liver metastases was achieved. By the time of submission of this paper, the patient's OS time had exceeded 9 years. This strategy may help improve the resectability of initially unresectable CRLM and prolong OS.

FOOTNOTES

Author contributions: Tan XR and Wang S were the patient's oncologists, reviewed the literature, and contributed to drafting the manuscript; Li J and Wang S were responsible for revising the manuscript for important intellectual content; Chen HW and Jiang N reviewed the literature and contributed to drafting the manuscript; Wang ZB and Luo W analyzed and interpreted the imaging findings; all authors issued final approval for the version to be submitted.

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ORCID number: Xiao-Rong Tan 0000-0002-1109-9427; Juan Li 0000-0002-0015-9682; Hua-Wei Chen 0000-0002-5182-9797; Wei Luo 0000-0002-8310-0319; Nan Jiang 0000-0002-4299-7481; Zheng-Bo Wang 0000-0001-8050-7570; Shuai Wang 0000-0002-9168-086X.

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