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COMMENTARY

Opportunities and challenges of multidisciplinary conversion therapy in advanced hepatocellular carcinoma

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Abstract: Surgical resection is still the most important radical treatment for primary hepatocellular carcinoma (HCC), but at present, the resection rate of newly diagnosed patients with HCC is only 30%. The recurrence rate of newly diagnosed patients suitable for surgical resection within 5 years after surgery is as high as 40%∼70%. Low initial resection rate and high postoperative recurrence rate are important reasons restricting the overall treatment effects of HCC in China. Under this background, effectively improving the resection rate of HCC and reducing the postoperative recurrence rate have become the key topics to improve the treatment effects of HCC. Some initially unresectable HCC patients may have access to surgery through conversion therapy. Conversion therapy, which mainly involves the combination of local, systemic, and multiple treatment strategies, offers hope for patients with advanced HCC. But there are still some patients who do not benefit from conversion therapy. So, how to improve the conversion success rate is still one of the challenges that clinicians need to solve.

Keywords: hepatocellular carcinoma, conversion therapy, multidisciplinary therapy

Commentary on hot topics

Primary hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China [1]. According to China's National Cancer Center, it ranks fourth in the number of new cases of all types of cancers, fifth in the incidence, and second in the number of deaths and mortality [2, 3]. Recently, surgical resection is the main means of obtaining radical treatment for HCC, but due to the poor health examination consciousness of many patients in China, and the clinical symptoms of early HCC patients are not obvious, 70%∼80% of patients are in the middle and late stage at the first diagnosis, lose the opportunity for surgery, and the prognosis is very poor [4]. Therefore, the concept of conversion therapy came into being, which is defined as the transitional treatment means, such as interventional therapy, radiation therapy, chemotherapy, targeted therapy and immunotherapy, for patients with middle and advanced tumors with potential surgical resection, to control the development of tumors, reduce the clinical stage of tumors, and finally achieve surgical standards [5–7] (Figure 1). It can also refer to patients who are not suitable for liver transplantation and meet the criteria for liver transplantation treatment after conversion therapy and get the opportunity for transplantation. During conversion therapy, multi-disciplinary treatment (MDT) is recommended to regularly evaluate the effects of conversion therapy. After the transformation of advanced HCC, it is more necessary to conduct a comprehensive and detailed evaluation of patients and develop a safe and feasible surgical resection plan [7, 8].

The effects of single drug treatment for HCC are poor and the conversion success rate is low. Hence, the combined treatment mode has become a trend. With the development of targeted drugs and immune drugs, conversion therapy has become a feature of the clinical treatments of advanced HCC in China, and a large number of clinical studies and methods are ahead of the international [9–12]. A retrospective study evaluated the clinical efficacy of lenvatinib combined with transhepatic arterial embolization (TAE) with or without pabolizumab in initial unresectable HCC. The results showed that the objective response rate (ORR) of pabolizumab plus lenvatinib combined with TAE was 47.1%, and the operative conversion rate was 25.7%, which was

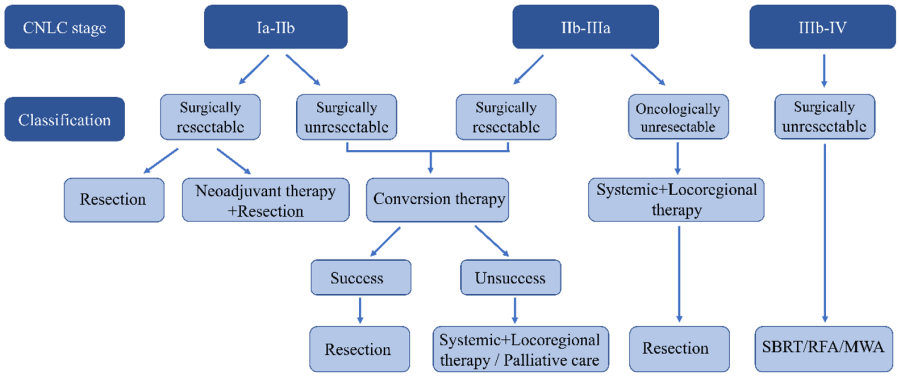

Figure 1 The roadmap for conversion therapy. CNLC, China liver cancer; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation; MWA, microwave ablation.

significantly higher than that of lenvatinib combined with TAE [13]. The results suggest that tyrosine kinase inhibitor (TKI) [14] combined with TAE combined immunotherapy can further improve the success rate of conversion therapy. Zhu et al. [15] showed that TKI combined with programmed cell death protein 1 (PD-1) in the treatment of initially inoperable HCC patients, 10 patients received R0 resection on average 3.2 months after the start of treatment, accounting for 15.9%, and 6 of them achieved pathological complete remission. This suggests that combined surgery after drug conversion therapy does provide long-term survival benefits. Lin et al. [16] included 30 patients receiving immunotargeted therapy combined with interventional therapy. There were 18 patients who achieved complete remission, 7 patients achieved partial remission, and the surgical conversion rate was 30%. Notably, it is suggested that the combination of cabozantinib and nivolumab improved the resection rate in patients with advanced HCC, thereby prolonging their recurrence free survival [17].

Ma et al. divided stage IIb/IIIa HCC patients into a group with surgery alone and a group with surgery after conversion therapy, and found that recurrence-free survival was significantly higher in the latter group. A Phase I clinical study of Renvastinib combined with pabolizumab in the treatment of unresectable HCC showed PFS and ORR of 9.3 months and 46.0%, respectively [18]. Other combination approaches are also being tried, such as targeted combined targeted therapy, double immunotherapy, or immunotargeted therapy combined local therapy [19, 20]. There may be synergies between different targeted agents, such as gefitinib, which enhances the anti-tumor effects of lenvatinib, and multiple data suggest that combinations of different immune checkpoint inhibitors also improve clinical outcomes [21–23]. In addition, although local treatment has limited therapeutic effect on advanced HCC patients, it can improve the conversion success rate of systematic treatment and prolong the survival time of patients. Therefore, even in the era of molecular and immunotherapy, local treatment such as transarterial chemoembolisation (TACE) and hepatic artery infusion chemotherapy (HAIC) is still an important means of HCC treatment [24–26].

A number of previous studies have shown that the combination of local interventional therapy plus targeted therapy and immunotherapy has better efficacy and is the most commonly used program in conversion therapy at present [27, 28]. He et al. [29] indicated that sorafenib combined with FOLFOX HAIC improved overall survival compared to sorafenib and had acceptable toxic effects in patients with HCC and portal vein invasion. Chang et al. [30] compared HAIC plus lenvatinib combined with PD-1 regimen with lenvatinib plus PD-1 regimen in high-risk advanced HCC patients, and found that the median survival and ORR of patients treated with the former regimen were significantly improved. Liu et al. [31] reported that patients treated with TACE plus lenvatinib in combination with camrelizumab reported the ORR of 68.2% in the first month and 72.7% in the third month. Zhang et al. [17] also confirmed that interventional therapy combined with immunotargeted therapy can improve the conversion surgery rate of unresectable HCC. In addition, another study showed that the combination of immunotargeted therapy and HAIC achieved a great ORR while maintaining controllable toxic side effects [32]. Chen et al. [13] also confirmed that the combination of HAIC, lenvatinib, tislelizumab and TAE is feasible and safe for HCC patients with portal vein tumor thrombus and significant tumor load.

Many studies [33–35] have reported that the common side effects of conversion therapy with immunotargeted therapy include hypertension, hypothyroidism, adverse reactions of digestive tract, thrombocytopenia, immunosuppression, skin lesions, etc. How to balance the side effects

and efficacy of drugs is an urgent clinical problem. Chu et al. [36] reported a case of one patient with giant advanced HCC who underwent successful surgery and achieved pathological complete remission after treatment including antiviral therapy, immunotargeted therapy, TACE, and HAIC. Although the tumor was successfully resected, the side effects of conversion therapy such as diarrhea, hypothyroidism, and neutropenia also seriously affected his quality of life.

However, the ultimate goal of conversion therapy is to improve the prognosis of patients, not simply to achieve radical resection. Therefore, for some patients with good conversion effects and stage decline reaching technical and oncologic resectable standards, how to decide the next treatment plan is an urgent evidence-based problem at this stage. For the evaluation of patients with advanced HCC, the indications, treatment modalities, and success criteria of conversion therapy are controversial, and there is still no conclusion as to which mode of local therapy or multi-mode sequential conversion therapy combined with multiple modalities should be selected for different patients. Moreover, the timing of surgery and safety management of conversion therapy also need further studying.

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Conflict of interest

The authors declare that they have no conflict of interest.

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