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Advances in Conversion Therapy for Primary Unresectable Hepatocellular Carcinoma

Xinhua Wu, Zhengrong Shi

Department of Hepatobiliary Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: shizr@hospital.cqmu.edu.cn

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Abstract

Primary liver cancer is one of the most common malignant tumours in the world, and according to statistics, about half of liver cancers occur in China, which seriously threatens the lives and health of people around the world, especially in China. Hepatocellular carcinoma is the most common type, accounting for about 90 per cent of primary liver cancers. Most patients are asymptomatic in the early stage and fail to pay attention to it. Most of the patients are in the middle or late stage when they are first diagnosed, and only 20% - 30% of them can receive radical hepatectomy. Patients are through the treatment to make the tumour shrinkage and downstaging, to achieve the condition of resectable, that is, the conversion treatment. Conversion therapy has great potential for development and has now become an indispensable treatment for intermediate and advanced hepatocellular carcinoma. However, there are various treatment options for conversion therapy, no uniform guidelines to guide clinical selection, and the overall conversion rate is still low, so it is particularly important to explore appropriate conversion therapy options. This article mainly describes the existing conversion therapies, hoping to provide help and ideas for exploring the best conversion therapies in the future.

Keywords

Hepatocellular Carcinoma, Transarterial Chemoembolization (TACE), Hepatic artery Infusion Chemotherapy (HAIC), Targeted Therapy, Immunotherapy

1. Introduction

Primary liver cancer is one of the most common malignant tumours globally, ranking 6th in incidence of malignant tumours globally [1]. It is estimated that

about half of all liver cancers occur in China [2]. This is a serious threat to the lives and health of people all over the world, especially in our country. Primary liver cancer is broadly classified into hepatocellular carcinoma, cholangiocellular carcinoma and mixed liver cancer, of which hepatocellular carcinoma is the most common type, accounting for about 90 per cent of primary liver cancers [3]. As hepatocellular carcinoma has an insidious onset and most patients are asymptomatic in the early stage, patients fail to pay attention to it, and most of the patients are already in the middle or late stage when they are diagnosed for the first time, and only 20% - 30% of the patients can receive radical hepatectomy. Therefore, its 5-year survival rate is only 15 per cent [4]. Hepatic resection is the only independent prognostic factor associated with overall survival [5]. It is especially important to improve the survival rate of patients with intermediate and advanced hepatocellular carcinoma. With the continuous development of interventional therapy, especially targeted therapy and immunotherapy, a lot of patients have their tumours shrinkage and downstaging to reach the condition of resectability through treatment, that is, the conversion treatment. Previous studies have shown that the 5-year survival rate of patients undergoing surgical resection after conversion therapy is the same as the 5-year survival rate of patients undergoing direct radical surgical resection [6] [7]. The results of a retrospective study that included 831 patients with first-time unresectable hepatocellular carcinoma showed that patients who were surgically resected after conversion therapy were able to achieve a greater benefit than those who continued with their current treatment, with a significantly higher overall survival time and 5-year survival rate [7]. Another study of conversion therapy with the next combined regimen similarly showed that its 3-year survival rate was significantly higher in patients who underwent surgery after conversion than in those who did not undergo surgical resection ($p = 0.009$) [8]. Conversion therapy has great potential for development and has now become an indispensable treatment for intermediate and advanced hepatocellular carcinoma. However, there are various treatment options for conversion therapy, no uniform guidelines to guide clinical selection, and the overall conversion rate is still low, so it is particularly important to explore appropriate conversion therapy options. Except for some intermediate and advanced patients who have the opportunity to undergo radical hepatectomy, the treatment of intermediate and advanced hepatocellular carcinoma is mainly based on local therapy and systemic therapy. Local treatment is mainly based on transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), etc. Previous studies have confirmed the role of TACE and HAIC in anti-tumour and prolonging the survival time of patients [9]. Systemic therapy mainly includes targeted therapy and immunotherapy. This paper focuses on the choice of strategies for the conversion therapy of middle and advanced unresectable hepatocellular carcinoma.

2. TACE

TACE is the most classic interventional treatment for hepatocellular carcinoma,

in which iodinated oil containing chemotherapeutic drugs such as cisplatin and pirarubicin is injected into the blood-supplying arteries of the liver tumour to block the blood-supplying arteries, and at the same time, the high concentration of chemotherapeutic drugs plays a certain role in killing the tumourcells [10] [11] [12]. The use of TACE for the conversion therapy of moderately advanced hepatocellular carcinoma dates back to the 1990s, with several studies using TACE to treat unresectable HCC, with tumour shrinkage and downstaging after treatment and access to surgical resection [7]. The results of several RCTs have similarly shown that TACE is useful for downstaging unresectable hepatocellular carcinoma at initial diagnosis to reach surgical condition [13]. This demonstrates the feasibility of TACE for the conversion therapy of patients with hepatocellular carcinoma. Although there is a large benefit to patients after conversion therapy, the conversion rate is low with TACE alone, approximately 8-18 per cent [14]. Therefore, the use of TACE alone for translational therapy is less common nowadays, but TACE is still the foundation and core of comprehensive treatment for intermediate and advanced hepatocellular carcinoma [15].

3. HAIC

HAIC has been greatly underestimated earlier due to misconceptions. Japan and South Korea use cisplatin-based chemotherapeutic agents for perfusion chemotherapy, and China mainly uses oxaliplatin + fluorouracil-based chemotherapeutic agents, and several studies have affirmed the efficacy of HAIC in intermediate and advanced hepatocellular carcinoma [16]-[21]. With the increasing research on HAIC confirming its role in the conversion therapy of intermediate and advanced hepatocellular carcinoma, it has been included in the guidelines for the treatment of hepatocellular carcinoma [22]. It has become one of the commonly used interventional treatments in Asia, but is still not recognised in Europe and America [23]. Several studies have demonstrated greater conversion efficiency with HAIC versus TACE. One study demonstrated a higher conversion rate (23.9% vs 11.5%, $P = 0.004$), longer progression-free survival (PFS) (9.63 vs 5.40 months, $P < 0.001$), and higher remission rate (mRECIST: 48.4% vs 32.7%, $P = 0.004$) in the group that received HAIC compared to the TACE treatment group, the results were from patients with giant hepatocellular carcinoma, diffuse hepatocellular carcinoma and hepatocellular carcinoma combined with portal vein thrombosis, and further studies are still needed to see if there is better efficacy than TACE in other hepatocellular carcinomas with a much lighter tumour load [24]. Another study also suggested that the HAIC group showed a higher tumour remission rate (52.6% vs. 9.8%, $P < 0.001$) and conversion efficiency (26.3% vs. 7.3%, $P = 0.033$) compared to the TACE group [25]. In several studies, HAIC has been shown to have advantages over TACE in conversion therapy, with a low incidence of adverse events, elimination of embolic syndrome and the possibility of ectopic embolism, and a simpler surgical procedure that requires only oversampling of the larger hepatic arteries [26] [27]. Less im-

pact on subsequent surgical treatment, TACE is more likely to cause an inflammatory response, especially for tumours protruding from the surface of the liver, which are prone to form adhesions with the surrounding tissues and organs, increasing the difficulty of the surgery, and the damage to the normal hepatic tissues is greater, increasing the likelihood of postoperative microhepaticsyndrome [28].

4. Targeted Combination Immunotherapy

In recent years, with the continuous research on hepatocellular carcinoma, targeted therapy and immunotherapy have emerged. In targeted therapy, sorafenib and lenvatinib have become the first-line therapeutic drugs for hepatocellular carcinoma. In immunotherapy, karelizumab and tirilizumab have become the commonly used drugs for treating hepatocellular carcinoma in the clinic. However, single drugs are seldom used as treatment options in current treatment programmes aimed at conversion. The results of clinical studies on targeted combination immunotherapy for hepatocellular carcinoma are relatively satisfactory, and targeted combination immunotherapy has a good synergistic effect. A high-quality randomised clinical trial demonstrated that when using sindilizumab in combination with bevacizumab group (n = 380) versus sorafenib group (n = 191) at conversion therapy, the combination group achieved an objective remission rate (ORR) of approximately 30%, with a significantly better median progression-free survival and overall survival than sorafenib (median PFS: 4.6 months [95% CI 4.1 - 5.7] vs. 2.8 months [95% CI 2.7 - 3.2]; OS: median not reached [95% CI not reached-not reached] vs. 10.4 months [95% CI 8.5-not reached), no less than that of TACE treatment or radiotherapy alone, and serious adverse events during treatment were in the acceptable range, suggesting an important place in conversion therapy [29]. In another phase 3 clinical trial on 336 patients in the atilizumab-bevacizumab group versus 165 patients in the sorafenib group, the 12-month overall survival rate was 67.2% (95% CI 61.3 - 73.1) in the atilizumab-bevacizumab group, and 54.6% (95% CI 45.2 - 64.0) in the sorafenib group, which affirms the combination therapy in the The efficacy of the combination therapy in the conversion therapy of intermediate and advanced hepatocellular carcinoma, and its adverse events are not significantly different from sorafenib treatment alone, the main adverse effect is hypertension, which is now the guideline as the first-line treatment option [30]. Lu Shichun *et al.* conducted a prospective study of targeted combination immunotherapy for the conversion of intermediate and advanced hepatocellular carcinoma combined with cancer embolism, with a conversion success rate of 51.0%, and 15 patients underwent surgical resection after successful conversion, with a 1-year recurrence-free survival rate of 61.1% [31]. A clinical trial in the United States using cabozantinib in combination with nabulizumab to treat patients with hepatocellular carcinoma included 15 patients, 12 of whom were successfully converted and underwent surgical resection, a conversion rate of 80 per

cent, 5 out of the 12 patients suggested a significant pathological response [32]. All of these findings demonstrate the place of targeted combined immunotherapy in the conversion therapy of hepatocellular carcinoma. It also lays the foundation for local therapy combined with systemic therapy in the future.

5. Local Therapy + Targeted Combination Immunotherapy

The emergence of targeted therapy and immunotherapy has provided great help in the treatment of hepatocellular carcinoma, and local therapy combined with systemic therapy has gradually become the main treatment modality for unresectable hepatocellular carcinoma in the intermediate and advanced stages. The results of a multicentre, randomised controlled trial [33], presented at the ESMO Annual Meeting 2023, showed that HAIC in combination with regorafenib and immunotherapy was effective in increasing the objective remission rate (ORR) compared to regorafenib in combination with immunotherapy and significantly prolonged the duration of overall survival (OS) in patients who received second-line therapy. And several previous studies have shown that topical treatments combined with systemic regimens have better efficacy and provide greater benefits to patients than single treatment regimens [34] [35] [36] [37]. Two prospective single-arm studies have analysed the efficacy of TACE-HAIC combined with sorafenib and HAIC in combination with lenvatinib and treprostinil in the treatment of intermediate to advanced hepatocellular carcinoma suggest excellent therapeutic outcomes [7]. This phenomenon also applies in conversion therapy. A study of HAIC in combination with lenvatinib and treprostinil monoclonal antibody versus lenvatinib alone in the conversion therapy of hepatocellular carcinoma enrolled 157 patients, 71 in the combination group and 86 in the lenvatinib group, and showed that the combination treatment group resulted in a higher rate of conversion resections (12.7% vs. 0%), a higher ORR (not reached vs. 11 months, $P < 0.001$), a higher tumour response rate (mRECIST: 67.6% vs. 16.3%, $P < 0.001$), and grade 3/4 adverse events in the combination therapy group were also in the acceptable range, with the main adverse events being neutropenia (8.5% vs. 1.2%), thrombocytopenia (5.6% vs. 0) and nausea (5.6% vs. 0%) [38]. Combinations between local therapies can also have good efficacy and translational ability, the most common combinations of local therapies are TACE in combination with HAIC or TAE in combination with HAIC. Li *et al.* investigated the efficacy of TACE-HAIC ($n = 41$) versus TACE alone ($n = 42$) in the conversion of intermediate to advanced stage first unresectable hepatocellular carcinoma [39], and the conversion rate of the former was significantly higher than that of the latter (48.8% vs 9.5%, $P < 0.001$), and the rate of grade 3/4 adverse events was similar in both groups ($P > 0.05$). Yichuan Yuan *et al.* included 743 patients with hepatocellular carcinoma combined with PVTT who were treated with either TACE-HAIC combination targeted immunotherapy or TACE alone [40], and the overall survival and progression-free survival were significantly higher in the combination therapy group than in the alone TACE group (OS, unreached median overall survival vs. 10.4

months, P < 0.001; median progression-free survival. 14.8 months vs. 2.3 months, P < 0.001), and the conversion rate was higher in the combination therapy group (46.3% vs. 4.5%, P < 0.001). Currently there are various options for local therapy combined with systemic therapy, and there is no universally accepted treatment protocol. Prospective studies are ongoing and more research is needed to validate their efficacy in conversion therapy.

6. Conclusion

Conversion therapy has become one of the important treatment modalities for unresectable hepatocellular carcinoma. However, the optimal treatment plan for conversion therapy is still controversial, and most of the current studies are small-sample retrospective studies. It is hoped that more large-sample, multi-centre prospective studies will be carried out in the future to explore the treatment plan with the greatest benefit to patients, so that more patients with unresectable hepatocellular carcinoma of intermediate and advanced stages can benefit from this treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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