Mini-Review

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Conversion therapy and maintenance therapy for primary hepatocellular carcinoma

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SUMMARY The preferred treatment for hepatocellular carcinoma (HCC) is surgery, which is the only way to achieve long-term survival and even a cure. However, the vast majority of patients with liver cancer in China are already in the middle to advanced stage of the disease and no longer have the opportunity to undergo surgery. The goal of conversion therapy is to transform unresectable advanced liver cancer or potentially resectable liver cancer into resectable cancer, so it has become a topic of interest in the treatment of advanced liver cancer. Common modalities of conversion therapy are: local treatment (TACE, TARE, or HAIC), systemic treatment (targeted therapy alone or combined with immunotherapy), and a therapeutic alliance (TACE combined with radiation therapy, TACE combined with targeted therapy, HAIC combined with targeted therapy, or HAIC combined with targeted therapy and immunotherapy). The plan for maintenance treatment after conversion therapy is determined based on the outcome of conversion therapy to obtain the best survival benefit for patients.

Keywords hepatocellular carcinoma, conversion therapy, maintenance therapy, China

1. Introduction

Hepatocellular carcinoma (HCC) is the second most common malignant tumor in China; about half of the new patients with HCC worldwide are Chinese, and approximately 300,000-400,000 people die from HCC each year (*1,2*). A survey of the current status of treatment for HCC in China indicates that most patients with HCC are already in the middle to late stages of the disease when diagnosed and no longer have the chance to undergo surgery (*3*). In the past, systemic treatment had limited effectiveness, and the emergence of targeted and immunotherapy drugs over the last two years has brought hope for the non-surgical treatment of HCC. In this context, several old terms from other fields have become topics of interest in the field of liver cancer treatment: downstaging therapy, conversion therapy, and neoadjuvant therapy. The aim of the current review is to provide some ideas for conversion treatment strategies and updates for HCC guidelines in China in this new era by systematically discussing the definitions of these terms, the related treatment modalities, and the subsequent treatment strategies.

2. Downstaging therapy and conversion therapy

Downstaging therapy is a method of turning an inoperable tumor in an advanced stage into an operable tumor in an earlier stage via systemic or local treatment. The term was first used in liver transplantation for HCC. As an example, patients who fell outside the Milan criteria and were not eligible for priority liver transplantation (United Network for Organ Sharing (UNOS) stage T3) were treated locally (transhepatic artery chemoembolization (TACE), ablation, *etc*.) to shrink or reduce the number of tumors to meet the Milan criteria (UNOS stage T2), and then transplantation was performed (*4*). The prognosis of successful liver transplantation was similar to that of a standard stage I liver transplantation. Conversion therapy is the conversion of an otherwise unresectable cancer into a surgically resectable one by means of systemic or local treatment. However, conversion therapy is again not equivalent to downstaging therapy. For example, HCC involving the main trunk of the portal vein or the main trunk of the superior mesenteric vein is BCLC stage C, meaning it is inoperable or unsuitable for surgical resection, but through conversion therapy, the tumor thrombus is reduced to the branch of portal vein and then operated on. If the tumor thrombus disappears completely after conversion therapy, it changes from BCLC stage C to BCLC stage B or A, and then conversion therapy lowers the tumor stage, so conversion therapy can be regarded as a part of

downstaging therapy. In the treatment of HCC in particular, liver resection is the goal of treatment rather than liver transplantation, so conversion therapy has greater practical value in clinical terms. Although the use of conversion therapy (including the combination of targeted therapy, immunotherapy, and interventional therapy) in the treatment of advanced HCC is still in its infancy, it has become a topic of interest in the treatment of advanced HCC because it can reduce the tumor size and focal necrosis, which can convert unresectable or potentially resectable HCC into radically resectable HCC.

3. Common modalities of conversion therapy

In 1993, Sitzmann & Abrams (*5*) were the first to report on unresectable cancer in 14 patients that was converted to resectable cancer after radiotherapy combined with chemotherapy. This opened the door to down-staging conversion of HCC. Various approaches subsequently emerged, including local and systemic treatments and more often a combination of the two.

3.1. Local treatment

Most commonly used local treatments include TACE, transhepatic artery radioembolization (TARE), and hepatic artery infusion chemotherapy (HAIC). TACE has been widely used in the treatment of mid- to late-stage HCC. Cancer in about 8-18% of patients is converted into an operable form after TACE treatment, and the 5-year survival rate of patients treated with surgery after downstaging TACE may be as high as 24.9-57%, and an even longer survival has been achieved in some patients (*6*). TACE has yielded long-term clinical results and offered a chance to those patients with HCC who were ineligible for radical surgery when initially diagnosed. TARE, which has 2 actions to kill a tumor, usually uses yttrium-90 as an embolic agent. Of 35 patients with UNOS stage T3 cancer, Kulik *et al*. (*7*) reported that TARE treatment successfully downstaged the cancer to T2 in 19 of 34 patients (56%) and that cancer in 23 (66%) of the 35 patients was downstaged to the extent that the patients were eligible for RFA or resection, creating a bridge to surgical procedures and yielding better results. In a recent study (*8*), however, only 9% of patients with HCC who were treated with TARE underwent liver transplantation (LT) or liver resection (LR). However, a promising result of that study is that the OS was 47 months while survival rates at 1-, 3-, and 5-years reached 97, 86, and 86%, respectively. Although the conversion rates differ considerably among studies, the long-term outcomes are consistent (*7-9*), suggesting that as long as conversion is achieved, the prognosis should be as good as that for patients undergoing radical resection following initial diagnosis. A point worth noting is that the extent of tumor necrosis still increases 3-6 months after TARE due to the lagging effect of radiotherapy on tumor cell killing, so repeated use of TARE is not required within 6 months.

HAIC has not been validated in large-scale randomized clinical trials, and thus guidelines on liver cancer from the American Association for the Study of Liver Diseases (AASLD), the National Comprehensive Cancer Network (NCCN), the European Society of Liver Diseases (EASL) and the Asia-Pacific Association for the Study of the Liver (APASL) (*10-13*) do not consider HAIC to be a recommended treatment for advanced HCC. However, HAIC has been used in Asia, and especially in Japan and South Korea, as an approach that can improve outcomes in advanced HCC and it is included in treatment guidelines (*14*). HAIC is greatly underestimated due to the small sample size in previous studies and the lack of large-scale randomized trials. In fact, HAIC is theoretically more effective than systemic chemotherapy for HCC because hepatic arterial infusion of anticancer drugs allows direct delivery of high doses of drugs to highly vascular HCC, including those micro metastases that cannot be detected with imaging and that may not have an obvious arterial blood supply. The intrahepatic first-pass effect results in lower systemic levels of HAIC drugs than systemic administration, reducing toxic effects and adverse events. In a randomized phase III study (9810) announced at ESMO 2020, HAIC (oxaliplatin, fluorouracil, and folinic acid) *vs*. hepatic artery chemoembolization for unresectable HCC with TACE resulted in a significant difference in the surgical conversion rate of 23.8% in the HAIC group *vs*. 11.5% in the TACE group ($p < 0.004$).

3.2. Systemic treatment

Sorafenib was effective as the first first-line standard systemic therapeutic agent for advanced HCC that was unresectable when diagnosed. Since then, many other promising drugs, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors, have been developed, making significant advances in systemic therapy for liver cancer. However, a single agent yields limited clinical results. The overall response rate (ORR) after sorafenib monotherapy was only 3.3% (*15*), that for cabozantinib was 4.0% (*16*), and that for regorafenib was 6.5%. Lenvatinib, which is an inhibitor of VEGF receptors 1-3, FGF receptors 1-4, PDGF receptor α, RET, and KIT, is reported to have an ORR as high as approximately 18.8%, which is much higher than that of sorafenib (*17*). However, lenvatinib and sorafenib groups have a similar OS, and patients with a tumor occupying ≥ 50% of the liver, obvious invasion of the bile duct, or portal vein invasion at the main portal vein were excluded from that study, which may explain the difference in ORR. At ESMO 2019,

nivolumab was reported to have an ORR of 15.0% alone, and the ORR for pembrolizumab alone was 18.3%. In a multicenter randomized phase II trial, Qin *et al*. found that carrilizumab alone had an ORR of only 14.7% (*18*). Although these results from worldwide centers are interesting and promising, the level of effectiveness is insufficient to meet clinical needs. Thus, combination therapy may yield a higher ORR compared to monotherapy and may signal the advent of a new era of conversion therapy for advanced HCC. As announced at ASCO-GI 2020, a phase 1b clinical study on lenvatinib in combination with nivolumab in patients with unresectable HCC noted an ORR of 54.2% after lenvatinib in combination with nivolumab (ASCO-GI 2020, Ib (117)). As announced at the 2019 ESMO Congress, the latest data from a phase 1b study on pembrolizumab combined with lenvatinib for advanced HCC indicated that the combination had an ORR of 46.3% (2019 ESMO (747P)). Qin *et al*. found that carrilizumab combined with apatinib had an ORR of 44.4% (*18*). Prognosis has sharply improved for patients with advanced HCC and the low rate of liver-related adverse reactions with combination therapy has made subsequent surgery safer. As a result, targeted therapy combined with immunotherapy is now the most commonly used approach for the conversion of HCC. At the 2020 ASCO Annual Meeting, Sun *et al*. (*19*) reported on 60 patients with unresectable cancer who received targeted therapy with a small-molecule TKI combined with immune checkpoint inhibitors. The cancer in 11 (18.3%) of those patients was converted to resectable HCC. As announced at ESMO Asia 2020, a study by Zhang *et al*. (*20*) found that HCC with portal vein tumor thrombosis (PVTT) was converted to a surgically resectable form in 42.4% of 33 patients received targeted therapy with a small molecule TKI combined with immune checkpoint inhibitors. These two recent studies provide further evidence for the feasibility and effectiveness of combination therapy.

3.3. Other combined treatment modalities

3.3.1. TACE-based combined therapy

The role of external radiation therapy in the treatment of liver cancer has gradually been highlighted, and the effectiveness of radiotherapy for HCC has significantly improved due to precise positioning technology. It has become an important tool for the conversion of HCC, and especially for the control of a tumor thrombus. External radiation therapy is mainly combined with interventional therapy for the conversion of advanced HCC with portal vein and inferior vena cava tumor thrombi.

In 2017, Li and Zhou (*21*) reported 21 cases of HCC treated with TACE combined with sorafenib that were unresectable on initial evaluation. In this Chinese study, the 1-, 2-, and 3-year OS rates were 85.7, 71.4, and 57.1%, respectively; these rates were much higher than that for regular treatment such as TACE or sorafenib alone. An important point is that sorafenib was used as maintenance therapy after surgery, which may enhance the survival rate accordingly. Although sorafenib was unable to improve the prognosis for patients who underwent radical resection following initial diagnosis, its value as maintenance therapy for down-staged advanced HCC warrants more attention and related clinical trials should be conducted like those with other TKIs and immuno-agents.

3.3.3. HAIC-based combined therapy

In a retrospective cohort study, Hamaoka *et al*. (*22*) evaluated the survival benefit and safety of hepatectomy after down-staging with 3-dimensional conformal radiation therapy (3D-CRT) for major PVTT and HAIC for unresectable HCC. Seven of the 52 patients became eligible for surgery, and there was a significant difference in overall survival (OS) between the surgical and non-surgical resection groups ($p = 0.009$). In 2019, He *et al*. (*21*) reported a conversion rate of 12.8% in patients with unresectable HCC treated with HAIC in combination with sorafenib, indicating that HAIC-based combined therapy could also yield results as good as those of TACE-based therapies. A recent study by Shi *et al*. (*23*) announced at ESMO Asia in 2020 (*24*) found that HAIC plus targeted therapy and immunotherapy for advanced HCC had an ORR of 67.6% according to the mRECIST criteria, which is the highest of all combination regimens available and offers a new option for HAIC-based conversion therapy in the future.

Conversion therapy is currently performed using a variety of approaches and regimens, and conversion therapy for advanced HCC is currently being studied, but there is no higher level evidence to confirm which treatment option is best. Thus, close collaboration of multidisciplinary teams is essential, requiring individualized treatment plans tailored to the patient's condition or the skills and experience of the treatment teams. That said, the overall trend is towards combination therapy. The conversion rate of combined therapy is higher than that of monotherapy, and the efficiency of combined local and systemic therapy is higher than that of local or targeted therapy combined with immunotherapy. A goal-oriented treatment strategy, the aim of conversion therapy is to achieve radical surgical resection and obtain a higher conversion rate. The most potent combination therapy regimen may be used in the future as long as the patient's physical condition and liver and kidney function permit. This could include HAIC combined with small-molecule TKIs and immune checkpoint inhibitors or TACE combined with radiotherapy, TKIs, and immune checkpoint inhibitors.

4. Maintenance therapy after conversion therapy is determined by the outcome of conversion therapy

4.1. Tumor progression is stable or the tumor is in partial remission but there is still no possibility of surgical resection

If the first-line conversion option is to use a potent and efficient local and systemic regimen, then the second-line treatment option should be a combination therapy causing fewer and less severe adverse reactions or a monotherapy, such as a second-line targeted drug or a targeted drug combined with an immune checkpoint inhibitor. After all, the main treatment goal for patients at this point is no longer conversion to surgery but to prolong survival as long as possible.

If the patient's physical status and liver, kidney, bone marrow function are sufficient and conversion is not prolonged, then the current treatment can be maintained until yielding results. The tumor may shrink further with additional rounds of treatment and be downgraded to a resectable status; if the patient has already received sufficient rounds of conversional therapy and his or her physical strength or liver, kidney, and bone marrow function are no longer sufficient to tolerate a potent treatment regimen, then options in the event of failure should be considered.

4.2. Successful tumor conversion following radical surgical resection

There is currently no recommendations for postoperative adjuvant therapy in any guidelines on HCC, and the 2020 CSCO (*25*) guidelines for the management of primary HCC (which usually has a high risk of recurrence) recommend postoperative administration of TACE. Although the STORM study of targeted therapy as postoperative adjuvant therapy (as exemplified by sorafenib) yielded negative results (*26*), numerous subsequent studies have concluded that targeted agents would still have a survival benefit in HCC with a high risk of recurrence (*27,28*). With the increased availability of numerous targeted agents and immune checkpoint inhibitors, more postoperative adjuvant therapy options will emerge in the future, with single agents such as lenvatinib, regorafenib, and apatinib, and with immune checkpoint inhibitors such as PD-1 or PD-L1 antibodies, and even targeted combination immunotherapy. Numerous clinical studies on postoperative adjuvant therapy for HCC with a high risk of recurrence have been initiated, and these therapies include nivolumab monotherapy (NCT03383458), carrilizumab combined with apatinib (NCT03722875), and lenvatinib combined with TACE (the LANCE study). Those findings will surely provide a stronger basis for postoperative adjuvant therapy to treat HCC in the near future.

Conversion therapy for HCC has just emerged. There are various conversion protocols but no standard protocol, so there is no definitive postoperative maintenance therapy for cancer that has been successfully converted and treated surgically. However, information can be gleaned from more established procedures for perioperative treatment of colorectal cancer liver metastases. Perioperative treatment of resectable colorectal cancer liver metastases with a high risk of recurrence usually lasts six months, and the postoperative regimen is basically a continuation of the preoperative chemotherapy regimen. Colorectal cancer metastases that are initially unresectable need to be treated with a more potent and efficient combination of two or three drugs than neoadjuvant therapy. The post-conversion regimen is weaker than the preoperative regimen, such as using targeting drugs only if there is a clear therapeutic response and then continuing to use them after surgery or using a shorter course of chemotherapy or even performing an observational follow-up. If, therefore, a more potent and efficient combination therapy is used on advanced HCC preoperatively (such as HAIC combined with targeted small-molecule TKI therapy and immune checkpoint inhibitors, or TACE and radiotherapy combined with targeted small-molecule TKI therapy and immune checkpoint inhibitors), then targeted therapy combined with 1-2 rounds of TACE or HAIC therapy can be used postoperatively. For patients with a significant treatment response, targeted therapy and immunotherapy, or even targeted therapy or immunotherapy alone can be used.

Antiviral therapy targets the etiology of HCC, but all other postoperative adjuvant therapies including targeted therapy and immunotherapy are focused on early recurrence after surgery, so what is traditionally considered to be radical surgery is actually a palliative resection. While the main tumor is removed, there are already tiny metastatic lesions outside the resection area. As described in the literature, colorectal cancer may already have the potential to metastasize to the liver or lungs even when the primary focus is only the size of a pinpoint, and metastatic seeding usually occurs much earlier, years before diagnosis and surgery, when tumor metastasis is not yet clinically detectable (*25*). Progression in patients with HCC is more due to progression of an underlying liver disease (like cirrhosis) and the malignant transformation of high- and low-grade dysplastic nodules, which in turn become early-stage carcinomas. Thus, the presence of potential microscopic carcinomas that are undetectable on imaging is more likely. These micro metastases may not have an obvious arterial blood supply. In principle, HAIC should be more effective than TACE, and multi-targeted targeted drugs that are both anti-proliferative and anti-angiogenic are better than targeted drugs that are solely anti-angiogenic. Therefore, an additive approach to preoperative conversion therapy for HCC is adopted as much as possible, combining effective

Table 1. A summary of conversion therapy

Modality	
(1) Local treatment	Ttransarterial chemoembolization (TACE) Transarterial radioembolization (TARE) Hepatic artery infusion chemotherapy (HAIC)
(2) Systemic treatment	Targeted therapy combined with Immunotherapy: Due to the low rate of liver-related adverse reactions, it has become the most common treatment of conversion therapy.
(3) Therapeutic alliance	TACE combined with radiation therapy TACE combined with targeted therapy HAIC combined with targeted therapy HAIC combined with targeted therapy and immunotherapy
Outcomes	Maintenance Treatment Plan
(1) Tumor progression and conversion therapy failure	The maintenance treatment should be combination therapy or monotherapy with few adverse reactions to prolong survival as long as possible.
(2) The tumor was partially alleviated or stable, but there was no possibility of surgical resection	If the patient has received enough conversion treatment and physical strength or liver, kidney, or bone marrow function is not sufficient to continue, the maintenance treatment can be selected in light of the failed conversion therapy.
(3) Conversion therapy successful and radical resection	Surgery is still the core treatment for patients with HCC to obtain the best survival benefit.

therapies as long as patients tolerate them. If conversion and resection are successful, then a subtractive approach is adopted as much as possible, using fewer effective therapies as maintenance postoperative adjuvant therapy based on a full analysis of preoperative therapies with the best response (Table 1).

5. Conclusion

Surgery remains the core treatment for patients with HCC to achieve the best survival benefit. With advances in targeted immunotherapy as well as radiotherapy interventions, multimodal conversion therapies are being explored to improve the proportion of inoperable HCCs that are potentially resectable and to reduce the risk of recurrence with postoperative adjuvant maintenance therapy, thereby improving the long-term prognosis for patients with advanced HCC (shown in Table 1). However, the role of these treatment options needs to be further investigated due to the lack of high-grade evidence. Future research on conversion therapy and successive maintenance treatment should focus more on scientifically designed randomized controlled trials with large samples to identify biomarkers of effective response and mechanisms of drug resistance and to obtain sufficient data to ensure the optimal combination regimen and sequence of therapies.

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