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Exploration of Strategies for Liver Cancer Transformation Therapy

Lijing Liu*

College of Nursing and Rehabilitation, North China University of Science and Technology, Tangshan 063200, China
**Author to whom correspondence should be addressed.*

Abstract: ***Radical liver resection is the main treatment method to improve the prognosis of patients with early-stage liver cancer. Most liver cancer patients in China are already in the late stage at the time of initial diagnosis, losing the opportunity for surgical treatment. In recent years, with the increase of effective treatment methods for liver cancer, more and more patients have benefited from conversion therapy. Based on this, this article mainly explores effective strategies for the transformation therapy of liver cancer, in order to provide some reference for the development of liver cancer treatment.***

Keywords: Liver cancer treatment; Conversion; Strategy.

1. Introduction

According to the statistics in 2020, primary liver cancer ranked the second in cancer related mortality and the fourth in incidence rate. At present, the most effective treatment for hepatocellular carcinoma is still partial liver resection and liver transplantation surgery. In clinical diagnosis, most patients are found to have advanced symptoms, and usually only about 20% of patients have the opportunity for radical surgical resection. With the development of local and systemic treatments, some liver cancer patients can undergo curative surgical resection after non-surgical treatment, and achieve long-term efficacy comparable to patients who underwent surgical resection in the early stages. In recent years, with the continuous development of molecular targeted drugs and immune checkpoint inhibitors, combined with traditional local treatment models, many unresectable advanced liver cancers have gained the opportunity for radical surgery. Conversion therapy has also become a hot topic in current clinical research.

2. Summary of Liver Cancer Transformation Therapy

Liver cancer conversion therapy is an important treatment mode for unresectable liver cancer patients to achieve downgrading conversion resection, control tumor progression, and improve survival rate. Conversion therapy and neoadjuvant therapy have certain similarities and are easily confused in clinical practice. Both are preoperative adjuvant therapy strategies, but there are significant differences in the implementation targets and treatment outcomes. Neoadjuvant therapy refers to the treatment of initially resectable tumors with local or systemic therapy before surgery, in order to eliminate potential metastatic lesions and achieve a reduction in stage, increase R0 resection rate, reduce recurrence rate,

and improve survival expectations. It is mainly suitable for patients with mid-term liver cancer. Conversion therapy refers to the treatment of late stage patients who are initially unresectable. After high-intensity treatment, some tumor lesions show partial or even complete remission, obtaining the opportunity for conversion resection. Subsequently, sequential surgical resection is performed with the goal of curative R0 resection, thereby improving the survival expectations of these potential resectable liver cancer patients. In recent years, with the development and improvement of treatment methods, the objective response rate of liver cancer to transformation therapy has been continuously increasing. Meanwhile, the scope of conversion therapy is constantly expanding. If the lesion cannot be removed due to factors such as liver decompensation, insufficient residual liver volume, or late tumor staging, and the opportunity for surgical resection is obtained through treatment, it can be called conversion therapy. The inability to remove tumors caused by later tumor staging is the main factor affecting treatment efficacy and is an urgent problem that needs to be addressed in current translational therapy.

3. Local Treatment

The most commonly used treatment for advanced liver cancer that cannot be operated on is local treatment, which is currently the most effective method and the preferred treatment option in clinical practice. The commonly used conversion therapy methods include interventional therapy through the hepatic artery, as well as radiation therapy and local ablation therapy. The traditional hepatic artery catheterization embolization chemotherapy is currently a widely used treatment mode, which uses iodized oil as a carrier and mixes with chemotherapy drugs such as mitomycin, doxorubicin, or cisplatin to form an emulsion and inject it into the tumor supply artery. Then, permanent or absorbable embolization agents are used to embolize the corresponding artery, thereby causing tumor ischemia and necrosis. Through hepatic artery radiation embolization therapy, microspheres labeled with radioactive elements are injected into the hepatic artery. The microspheres accumulate and stay in the tumor site and blood supply artery, causing both radiation damage to the tumor and destruction of the blood supply artery, resulting in a double killing effect. In some cases, compensatory hyperplasia of the contralateral liver can also be induced, which is beneficial for the safety of subsequent liver resection. The commonly used radioactive element in clinical practice is yttrium-90, which can emit beta rays to induce tumor necrosis. Hepatic arterial infusion chemotherapy (HAIC) has gradually received attention in recent years, especially in Japan as a suboptimal treatment for unresectable locally advanced liver cancer, and is highly recommended in guidelines. In recent years, multiple studies have shown good objective response rates and long-term survival rates in the treatment of unresectable liver cancer using FOLFOX based chemotherapy regimens via hepatic artery infusion, gradually gaining attention from people.

4. Ablation Therapy

In the treatment of early liver cancer, ablation is crucial. It includes two methods: chemical ablation (ethanol, acetic acid, etc.) and physical ablation (radiofrequency, microwave, ultrasound, laser, freezing, etc.). For some early-stage liver cancer, the efficacy of radiofrequency ablation is almost the same as that of radical surgery. However, for patients with unresectable high-risk factors, the efficacy of ablation is currently unclear. A retrospective study included 29 patients with unresectable liver cancer accompanied by portal vein invasion. After treatment with high-power ultrasound focused ablation (HIFU), the objective remission rate reached 52.1%, indicating that ablation has certain potential for liver cancer transformation therapy. There are also research results showing that ablation has a good therapeutic effect on extrahepatic oligometastases, which can improve the survival status of patients with minimal trauma. For patients with small extrahepatic oligometastases (stage IIIb), ablation is a viable option. However, ablation cannot eliminate potential circulating tumor cells, and other

treatment options should be combined in the transformation strategy. Even if the transformation is successful, whether ablation can replace surgery still needs further research to verify.

5. System Therapy

Since Sorafenib was approved by the FDA for first-line clinical treatment of advanced unresectable hepatocellular carcinoma, there has been significant progress in the systematic treatment of liver cancer. Currently, various molecular targeted drugs and immune checkpoint inhibitors have been applied in advanced liver cancer. Due to the relatively low objective remission rate, there are not many patients who have successfully converted to the above-mentioned monotherapy and received surgical treatment, and most of them are reported as individual cases. Currently, conversion based treatments rarely use a single drug as the initial treatment plan. The clinical research results of combining molecular targeted drugs and immune checkpoint inhibitors are gratifying. The combination therapy has a good synergistic effect, significantly improving ORR and overall survival compared to sorafenib monotherapy. Among them, the ORR of pembrolizumab (anti-PD1 monoclonal antibody) combined with lenvatinib in phase Ib clinical trials reached 36.7%, and the ORR of at zolizumab (anti-PD-L1 monoclonal antibody) combined with bevacizumab (anti-EG-FR monoclonal antibody) in the treatment of unresectable liver cancer in phase III clinical trials of Imbrave150 reached 33.2%. The ORR of the combination therapy of molecular targeting and immune checkpoint inhibitors is almost close to the level of traditional TACE therapy, which provides us with a new strategy for translational therapy.

In summary, conversion therapy can enable the transformation and resection of some advanced liver cancer, achieving a prognosis for patients who have undergone radical resection that is not inferior to those who have undergone initial resection. However, at present, translational therapy also faces many challenges, such as the lack of unified staging standards for liver cancer and inconsistent inclusion criteria for different studies. At the same time, future clinical practice needs to integrate the treatment advantages of different disciplines, include potential benefit patients in standardized management, develop three-dimensional treatment plans, and thus improve the success rate of conversion.

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