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MINIREVIEWS

Progress in the treatment of pulmonary metastases after liver transplantation for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and is the third leading cause of cancer-related death. Liver transplantation (LT) has become a curative treatment for patients with HCC. However, recurrence and metastasis after LT are the main factors reducing long-term survival in patients, and the lung is the most common site of metastasis after LT for HCC, although metastasis to liver, para-aortic lymph nodes and renal periphery are observed. Thus, the treatment of pulmonary metastases after LT for HCC has become a hot research topic, the successful treatment of pulmonary metastases can significantly prolong the survival of LT patients. Although single conventional treatment (chemotherapy, surgery and external beam radiation therapy), immunosuppression, image-guided minimally invasive therapy (radiofrequency ablation, microwave ablation, cryoablation, and brachytherapy) and molecular targeted drugs have had a significant effect, patients do not have durable remission and the long-term survival rate is disappointing. Therefore, improving existing treatments and identifying a more effective combination therapy are important research issues in the prevention and treatment of pulmonary metastases after LT for HCC. The paper reviewed single conventional treatments, new treatments, and combination therapy, to provide a basis for the best treatment of these patients.

Key words: Liver transplantation; Progress; Treatment; Pulmonary metastases; Hepatocellular carcinoma

Core tip: The treatment of pulmonary metastases after liver transplantation for hepatocellular carcinoma has become a hot research topic. Although single conventional treatment (chemotherapy, surgery and external beam radiation therapy), image-guided

minimally invasive therapy (radiofrequency ablation, microwave ablation, cryoablation, and brachytherapy) and molecular targeted drugs have had a significant effect, patients do not have durable remission and the long-term survival rate is disappointing. Therefore, we reviewed single conventional treatments, new treatments, and combination therapy, to provide a basis for the best treatment of these patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, is the third leading cause of cancer-related death, and the incidence is high and increasing[1,2]. Liver transplantation (LT) is carried out to treat HCC, especially in the early stage[3]. However, due to extrahepatic organ micrometastases, which cannot be found by imaging and cancer cells present in the blood circulation before LT, the characteristics of liver cancer (microvascular invasion, low differentiation, allelic imbalance, genetic diversity), the stage (super Milan criteria) and the administration of immunosuppressive agents during and after LT[4], result in a high incidence of postoperative recurrence and metastasis (60%-100%)[5]. Tumor recurrence and metastasis obviously decrease the chance of long-term survival after LT for HCC[6,7], thus recurrence and metastasis are the greatest obstacles to successful HCC treatment.

Lung is the most frequent site of metastasis after LT, although metastasis to liver, para-aortic lymph nodes and renal periphery are observed[8]. The successful treatment of pulmonary metastases can significantly prolong the survival of LT patients[9]. Therefore, improving existing treatments and identifying a more effective combination therapy have become important issues in pulmonary metastases after LT for HCC. The purpose of this paper is to provide an overview of therapies for pulmonary metastases after LT for HCC. Therefore, we reviewed single conventional treatments, new treatments, and combination therapy, to provide a basis for the best treatment of these patients.

CONVENTIONAL TREATMENT METHODS

Chemotherapy and external beam radiotherapy

The administration of chemotherapy for lung metastases after LT is controversial. The United Network for Organ Sharing data indicate that 48% of HCC patients received adjuvant chemotherapy after LT[10]. However, the results of therapy have been disappointing, and pulmonary metastases response rates after single or multiple agent chemotherapy regimens were low, with the 1-year survival rate between 0% and 30%[11]. Lee *et al*[12] reported that the most commonly used chemotherapeutic regimens were administered to patients following LT for HCC, and the median time to progression was 7.0 wk (95%CI: 5.8-8.2) and the median overall survival was 16.6 wk (95%CI: 10.1-23.1). Roxburgh *et al*[13] also found that HCC was generally chemoresistant and results using systemic therapy were disappointing. In addition, patients after LT required long-term oral immunosuppressive drugs, as the vast majority of patients could not tolerate chemotherapy toxicity, which was also a problem when administering chemotherapy[14].

There has been some progress in the use of external beam radiotherapy (EBRT), particularly the use of three-dimensional conformal radiotherapy and the tomotherapy system, which have significantly increased the partial or complete remission rate of lung metastases[15]. Jang *et al*[16] reported that 30-57.6 Gy of radiation for lung metastases resulted in a complete response rate of 26.3%, and the overall survival rate at 1 year was 50.1%. Matsui *et al*[17] also showed that stereotactic radiotherapy, performed at the site of tumor location two years after radiotherapy, resulted in survival of the patient without recurrence. However, at the time of diagnosis, most patients have multiple pulmonary or systemic metastases[18]. Therefore, the future trend in radiotherapy for pulmonary metastases after LT for HCC is to increase the tumor area dose by screening patients cautiously and using advanced radiotherapy positioning technology, while reducing the scope of normal tissue irradiated and the incidence of radiation toxicity. EBRT has significant value for lung metastases after LT for HCC.

Surgery

Surgery has been accepted as the first treatment for pulmonary metastases after LT for HCC for some time. Studies have confirmed that surgery is effective, and survival is reported to be between 24% and 78% at 3 years, with median survival ranging from 21 mo to 29 mo[19,20]. However, surgical resection of isolated metastasis following LT for HCC is limited to a few studies or case reports worldwide[21,22]. Bates *et al*[23] reported that five patients who had pulmonary resection of metastatic HCC after LT, had an average survival period of 44 mo after transplantation and 28 mo after pulmonary resection, these survival times were similar to those of patients following metastasectomy after liver resection for HCC. A year later, Zhang *et al*[18] also reported five patients who underwent standard lobectomy or wedge resection, and their survival ranged from 3 to 53 mo, with an average survival period of 18 mo. Similarly, Togashi *et al*[24] described two cases with long-term survival following pulmonary metastasectomy for HCC recurrence several months after living donor

liver transplantation, with no signs of further recurrence 2 years and 4 years 5 mo after resection of the lung metastasis. These studies show that resection of pulmonary metastases is an effective treatment method. However, growth of metastatic tumors in the alveoli causes no or mild respiratory symptoms in the early stages of disease. At the time of diagnosis, lung metastases have usually already developed into multiple metastatic lesions, and most patients are denied the chance of surgical treatment[25]. Furthermore, due to immunosuppression and surgical trauma, lung lesions may recur after resection at any time, and possibly metastases in other organs. The rate of recurrence and metastasis in patients receiving immunosuppressive therapy is significantly higher than in those who do not receive immunosuppressive therapy, indicating that immunosuppressive therapy plays a major role in tumor recurrence and metastasis after LT[26]. Therefore, the value of surgery in the treatment of lung metastasis after LT for HCC should be confirmed by further prospective multi-center clinical studies.

NEW TREATMENT METHODS

Immunosuppression

More and more studies have confirmed that immunosuppressants [*e.g.*, mammalian target of rapamycin inhibitors (m-TORi)] have anti-transplant rejection and multiple anti-tumor effects after LT for HCC[27,28]. Kawahara *et al*[29] found that m-TORi can decrease the risk of recurrence after LT for HCC and have lower drug toxicities. Cholongitas *et al*[30] also showed that patients on m-TORi had significantly lower recurrence rates following LT for HCC, thus m-TORi may represent an alternative immunosuppressive regimen with antineoplastic effects. Moreover, the early use of m-TORi can significantly prolong survival time and delay tumor progression after LT[31]. Klintmalm *et al*[32] indicated that m-TORi may have benefits in the oncology setting and in relation to HCV-related allograft fibrosis, metabolic syndrome, neurotoxicity, and survival time. However, clinical studies have demonstrated that immunosuppressive agents can cause serious adverse reactions in patients such as pneumonia and thrombocytopenia[33]. In patients with pulmonary metastases after LT for HCC, most were in poor physical condition and were unable to tolerate further treatment. Therefore, further research on reducing the side effects of m-TORi and controlling further progression with combination therapy for pulmonary metastases after LT for HCC, will have significant clinical value.

Minimally invasive therapy

In recent years, due to the development of medical imaging, many patients with pulmonary metastases may also be treated with minimally invasive treatments, such as interstitial laser coagulation, cryotherapy, microwave ablation, percutaneous ethanol injection, radiofrequency ablation (RFA), and ^{125}I brachytherapy[34,35]. RFA uses thermal and non-thermal effects which are generated by RFA electromagnetic waves in a biological medium to solidify cancer tissue, and the local temperature can be higher than 90 ℃, which kills tumor cells quickly and effectively. RFA has been demonstrated to be a safe and valuable treatment option and is accepted as the best therapeutic choice for patients with unresectable HCC pulmonary metastases. Lencioni *et al*[36] reported that RFA results in a high proportion of sustained complete responses in properly selected patients with pulmonary malignancies, and is associated with acceptable morbidity. Hiraki *et al*[37] found that RFA for 83 pulmonary metastases resulting from HCC was effective and safe in selected patients, where the effectiveness rate was 92% and survival rate was significantly improved. Therefore, RFA improves survival in patients with limited metastatic lung disease[38]. In addition, ^{125}I brachytherapy has also been used for pulmonary malignant tumors with good efficacy. Zhang *et al*[39] reported that computed tomography-guided ^{125}I seed implantation was safe and well tolerated for treating lung tumors, with few complications, and the 1-, 3-year, and median overall survival were 68.7%, 20.8% and 17.4 mo, respectively. While the minimally invasive treatment of malignant lung tumors has significantly progressed, there are few reports on pulmonary metastases after LT for HCC. With further clinical studies, coupled with the advantages of minimally invasive treatment, such as safety, ease of use, few complications and minimal trauma, this will become a new treatment for pulmonary metastases after LT for HCC.

Targeted drugs

Sorafenib is a small molecular multikinase inhibitor of vascular endothelial growth factor (VEGFR)-2, VEGFR-3, platelet-derived growth factor-b, raf, Flt-3 and c-KIT. Studies have demonstrated the ability of sorafenib to inhibit tumor proliferation *via* the RAS-/RAF-signaling pathway and angiogenesis[40,41]. Sorafenib has been approved for the treatment of advanced HCC[42]. Kudo *et al*[43] reported 15 cases with complete remission following treatment with sorafenib in patients with advanced metastatic HCC, including multiple liver lesions, lymph node metastases, adrenal metastases, lung metastases and vascular invasion, which were completely absent after treatment, and three tumor markers (AFP, PIVKA-Ⅱ and AFP-L3) returned to normal values. In addition, sorafenib has also made a breakthrough in the treatment of HCC recurrence after LT. Sposito *et al*[44] found that sorafenib was associated with an acceptable safety profile and had a survival benefit in HCC patients suffering recurrence after LT, the recurrence time was 38.1 mo, living conditions were significantly improved after cancer recurrence (the median survival from recurrence was 21.3 mo), and the only factor associated with survival after HCC recurrence in multivariate analysis was treatment with sorafenib (HR = 4.0; P = 0.0325). Yeganeh *et al*[45] in a large single-center retrospective study found that

sorafenib was safe and well tolerated in patients with recurrent HCC following LT and may be associated with a modest survival benefit, the rate of survival at 3, 6, 9, and 12 mo was 100%, 80%, 71% and 62%, respectively. However, studies on the therapeutic value of sorafenib in pulmonary metastases after LT for HCC are rare, and only a few case reports were identified in the present review. Furthermore, serious adverse reactions have been observed, and some patients could not tolerate conventional doses of sorafenib and required dose reduction, which led to progression and deterioration of the disease or death[14,46]. Therefore, further investigations are needed to confirm the efficacy of sorafenib in the prevention and treatment of HCC after LT in international and multi-center randomized studies with a large sample size. Nevertheless, sorafenib is still a safe treatment and has a place in the treatment of pulmonary metastases after LT for HCC.

Comprehensive treatments

In clinical practice, it is difficult to achieve the desired results in patients with HCC lung metastases using a single treatment, therefore it is necessary to combine two or even more treatment methods. At present, reports on the combination therapy of pulmonary metastases after LT for HCC are rare. Sakamoto *et al*[47] reported one patient with HCC, multiple lung metastases and peritoneal metastasis. The patient was treated with a variety of methods including injection of ethanol, chemotherapy, and surgical resection, and although the patient died from cerebral infarction caused by tumor thrombus, the patient's quality of life for five years was significantly improved. Matsui *et al*[17] described one patient with HCC who underwent right hepatic lobectomy and was found to have right lung metastases two years later, and lobectomy after chemotherapy was ineffective. The left lung was then found to have metastasis, the patient received directional EBRT, and quality of life within two years was good with no further recurrences. Li *et al*[48] reported 8 patients with HCC who underwent LT and then were found to have lung metastases. All patients received brachytherapy combined with sorafenib therapy. The local control rates of multiple lung metastases after LT for HCC after 4, 6, 12, 18 and 24 mo were 92.2%, 82.4%, 76.2%, 73.3% and 72.2%, respectively, and the overall 1-, 2- and 3-year survival rates were 100%, 50% and 12.5%, respectively. These studies suggest that treatment of patients with HCC metastases after LT should be individualized, with comprehensive therapies, or combined methods with a variety of treatments according to the condition of the patient, to improve their quality of life and survival.

CONCLUSION

Recurrence and metastasis are major problems restricting long-term survival after LT, while single treatments have had some success, they still need further study. New treatment methods have also had remarkable success and have the potential to delay progression and prolong survival, however, this does not apply to all patients. Therefore, improving the existing treatments, using individual and combination therapy, is the future direction for the prevention and treatment of pulmonary metastases after LT for HCC.

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