

Analysis of treatment methods for liver cancer

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Abstract. Cancer is a challenging disease to treat and has resulted in numerous fatalities. Among these cancers, liver cancer accounts for an important proportion of deaths from cancer and has become one of the main causes of human death. To this end, the treatment of liver cancer is of utmost importance, and scholars worldwide are exploring ways to cure it. Currently, several liver cancer treatment methods have significantly advanced. Different regions have varying treatment methods for liver cancer patients, including targeted drug therapy like sorafenib and the use of viruses to destroy cancer tissue. It is crucial to summarize the advantages and disadvantages of different treatment plans as they are suitable for different patients. This research will analyze existing therapies used in the treatment of liver cancer, highlighting their present situation with deficiencies. The relevant achievements of scholars from different countries are discussed to function as a reference for the subsequent development of liver cancer treatment.

Keywords: liver cancer, treatment, application.

1. Introduction

The liver is one of the vital organs of the human body, responsible for storing hepatic sugar, de-oxidizing, and synthesizing secretory proteins. Various liver diseases, including hepatitis and cirrhosis, can affect these vital functions. Liver cancer is particularly lethal among all types of liver diseases. Hepatocellular carcinoma (HCC) belongs to a form of liver cancer that often develops as a result of due to chronic liver disease and cirrhosis. The areas with the highest rates of this phenomenon are generally North America, Oceania, and Europe, regardless of gender [1]. In 2012, it is the second leading cause of cancer-related death in men, and the occurrence rate of HCC among women is also increasing [1]. Therefore, studying the treatment of liver cancer is crucial.

In recent times, therapy for liver cancer has made significant progress due to the continuous development and advancement of science and technology. So far, different liver cancer treatment methods have been developed and achieved good application results. The common treatments for liver cancer include cytotoxic drug therapy, chemoembolization, and targeted drugs. However, to develop a more effective cancer treatment for HCC still faces some problems and limitations. For instance, in standard frontline therapy, sorafenib is used. Sorafenib is a multichines inhibitor that inhibits Raf-1 and other tyrosine kinases activity [2]. Sorafenib is the first targeted therapy approved for the treatment of advanced HCC patients with relatively preserved liver function. However, sorafenib has significant limitations. It should only be used in patients with advanced HCC whose liver function is well preserved [3]. In HCC patients with Child-Pugh grade B or C cirrhosis, there is insufficient evidence to support its use [3]. For this reason, some therapeutic methods have also been developed and used in the treatment of liver cancer, such as new treatment methods based on nanomaterials.

This research will analyze and discuss the current development for the treatment of HCC and the existing problems, including drug therapies and new treatments based on nanomaterials. The aim is to provide a reference for future therapy development for hepatocellular carcinoma.

2. Different types of liver cancer treatments

2.1. Drug therapy based on sorafenib

Sorafenib, a multichines inhibitor which can block the proliferation of tumor cells and angiogenesis [2]. The way it works is through inhibiting several tyrosine kinase receptors, such as vascular endothelial growth factor receptor 2 (VEGFR2) [2]. Following positive outcomes from a large randomized Phase III clinical trial, sorafenib approved for clinical use as a significant and effective treatment method for advanced renal cell carcinoma. Sorafenib was reported to block Raf kinase signaling in vitro, inhibit tumor cell proliferation, and induce apoptosis [2]. These results suggest that sorafenib is a highly effective drug for the treatment of advanced HCC.

Although randomized clinical trials have shown sorafenib to be a highly effective treatment for patients with advanced HCC, safety concerns remain. To assess safety, a prospective global trial was conducted to evaluate the safety of sorafenib in HCC patients, including Child-Pugh B patients who were not included in clinical trials [3]. The study found that while the effectiveness of sorafenib varied between patients, the overall safety and administration strategy remained consistent within the Child-Pugh subgroup [3].

2.2. Chemotherapy

Adriamycin (ADM) is a chemotherapy drug commonly used to treat liver cancer by inhibiting the growth of liver cancer cells. The MTT assay demonstrated that ADM inhibited the growth of human HCC cell lines MHCC97-L, HCCLM3 to varying degree. Although doxorubicin is an effective treatment, it is not suitable for all patients. Specifically, it is not the best treatment for patients with inoperable liver cancer. Studies have shown that using doxorubicin to treat those with inoperable liver cancer can cause fatal complications. The safety and efficacy of ADM (Adria Laboratories, Columbus, OH) in the treatment of unresectable HCC has been evaluated in a trial. 60 patients were randomized to receive an ADM 60-75 mg/m² every three weeks, while 46 patients received no antitumor therapy [4]. Median survival in the ADM group was 10.6 weeks, compared with 7.5 weeks in the group without anti-tumor therapy [4]. Doxorubicin was only associated with tumour regression in a small percentage of patients, however, fatal complications occurred in a quarter of patients [4]. The severity of neutrophilia resulting from sepsis is unpredictable, cardiotoxicity was observed in some patients who received doxorubicin at less than 500 mg/m² [4]. Therefore, it is concluded that ADM may not be the most suitable drug for treating inoperable HCC.

2.3. Oncolytic virus therapy

Oncolytic virus therapy is an innovative form of cancer therapy that uses viruses to optional attack and destroy cancerous tissue while leaving normal tissue unharmed [5]. The therapy achieves therapeutic effects by utilizing intrinsic anti-cancer treatment mechanisms to eliminate cancer cells through various means, including direct virus-mediated cytotoxicity and cytotoxic immune effects [5]. Talimogene laherparepvec (T-Vec) is a second-generation oncolytic herpes simplex virus type 1 (HSV-1) with GM-CSF combination [6]. The effectiveness of oncolytic virus therapy in inhibiting tumour growth has been investigated in a diverse of different studies. Phase III clinical trials have shown that local injection of T-Vec in advanced melanoma patients can effectively inhibit injected tumours grow and have systemic effects, thereby extending overall survival [6]. Two phase 1/2 clinical trials demonstrated that injecting T-Vec directly into tumors of patients with metastatic malignant melanoma resulted in complete resolution of the disease in 8 out of 50 treated patients, regardless of whether or not they received the injection [5].

These studies demonstrated that intratumoral administration of oncolytic viruses effectively initiate and enhance anticancer immunity. This also demonstrates the potential of oncolytic virus therapy to the public, providing evidence of its efficacy. Although oncolytic virus therapy shows promise in treating liver cancer, it still faces technical challenges. These include optimizing systemic viral transmission, promoting intra-tumor viral transmission and anti-cancer immunity, and

developing better model systems to accurately reflect human oncolytic virus therapy. Solving these problems is crucial for advancing oncolytic virus therapy.

2.4. Immunotherapy

T-cell-based immunotherapy is a novel therapeutic approach for HCC because of its immunogenicity. It delivers inhibitory signals through programmed death 1 (PD-1) and its ligands, PD-L1 and PD-L2, to adjust T cell activation and achieve a balance between tolerance and immunopathology. The immune response requires a specific and balanced response to foreign antigens and autoantigens to clear tumors and pathogens. Immune checkpoint pathway inhibitors, such as iprilimumab, have been shown to extend median overall survival in patients with advanced melanoma. In combination with gp100, median overall survival was 10.0 months compared to 6.4 months for patients treated with gp100 alone [7]. In previously treated patients with metastatic melanoma, the median overall survival for patients receiving ipilimumab alone was 10.1 months, and the mortality hazard ratio for all-cause mortality was 0.66 compared with gp100 alone [7]. Improvement in overall survival with use of immune checkpoint, demonstrating the potential of T cell-based immunotherapy. Recently, immunotherapy has made significant advances for the treatment of liver cancer. However, further research and improvement are necessary before it can be officially implemented in clinical settings. For instance, expanding the library of HLA Class I and Class II presenting TAA-specific T cell epitopes and studying the mechanism of T cell failure are crucial areas that require attention.

2.5. Other new treatments

ATP inhibitor 3-bromopyruvate (3-BrPA), is a potent inhibitor of cellular ATP production [8]. It can be delivered directly through the arteries to tumors located in the liver and cause a lethal rapid attack on most of them. When injected into a rabbit tumor implanted in the liver, 3-BrPA reduced the total number of living cells in the tumor to 10% and the treatment did not cause any noticeable damage to the animal or its major tissues [8]. This study presents a new potential use for a carefully selected chemical agent, 3-BrPA, which can have a significant impact on primary and secondary metastatic tumours when administered through a combination of arterial and systemic routes, without causing significant harm to the host [8]. This could be an attractive strategy for the suppression of the growth of liver cancers with a minimum of toxic side effect.

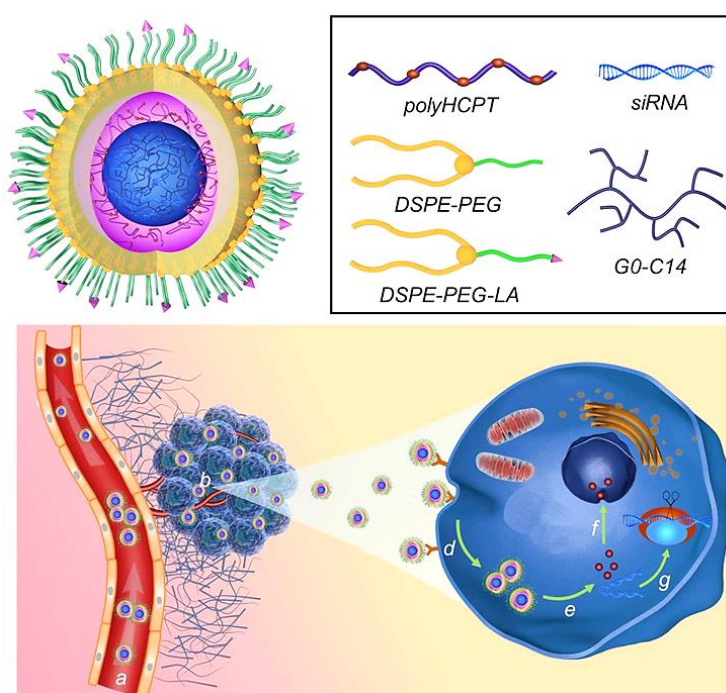


Figure 1. Targeted siRNA delivery and cancer treatment based on nanomaterials [9].

Nanoparticles (NPs) can be widely used for the systemic delivery of a variety of anticancer drugs, and this approach has several advantages, such as enhanced tumour accumulation [9]. Consequently, there is growing interest in NPs-mediated combination therapy as an effective means of treating cancer. But the clinical application of NPs-mediated combination therapy is limited because of complex preparation processes, which can cause changes in load levels and release kinetics between batches [9]. Additionally, the drug load is often unable to reach high levels when co-delivery NPs physically embed chemotherapeutic drugs [9]. Premature medicine release may also hinder clinical translation, the clinical translation remains challenging because of the difficulty in accurately controlling the loading of combination therapeutics to maximize therapeutic efficacy and the non-optimal NPs properties [9]. As shown in Fig. 1, a research team has developed a new REDOX reactive multi-precursor drug nanoplatform for the targeted delivery of siRNA and for synergistic cancer treatment. The developed NPs platform has a core of 10-hydroxycamptothecin (HCPT)-based polyHCPT, a shell of polyethylene glycol (lipid-PEG), and a surface modified with lactic acid (LA), after loading with siRNA and subsequent systemic delivery, the resulting NPs platform is able to target and accumulate in liver cancer cells in the tumor tissues by the specific recognition between the LA and asialoglycoprotein (ASGP) receptors [9]. Disulfide bonds in polyhcPT are broken by high glutathione concentration in the cytoplasm, which result in the rapid release of complete HCPT molecules and coated B-cell lymphoma 2 (Bcl-2) siRNA (siBcl-2), this process induces apoptosis by HCPT as well as silences anti-apoptotic genes in siRNA (siBcl-2), which synergistically inhibits tumor growth [9].

The mechanism of hyperthermia involves transferring a significant amount of heat to the tumour, raising its temperature above a specific threshold. This causes cancer cells to die due to enzyme changes. The duration of treatment, the temperature and the characteristics of the organ tissue affected determine the effectiveness of hyperthermia treatment. Currently, ultrasound and photothermal therapy are among the physical methods used to heat cancerous tissue, a crucial challenge in hyperthermia treatment is achieving sufficient heat concentration in a specific area to avoid unnecessary damage to surrounding healthy tissue [10]. Photothermal therapy is not a suitable option for deep tumors with a large volume due to its highly focused laser beams. The effect of the input power of a microwave antenna (MWAN) on HCC tumors has been investigated, where was injected with magnetic nanoparticles (MNPs). The first three minutes of ablation were performed using a microwave antenna with a frequency of 2.45 GHz and a power of 90 W, subsequently, after injection of MNPs, the effects of different MWAN input powers were investigated [10]. The results indicate that the optimized external magnetic field has the input microwave power is 35 W and a simulated intensity of 15 mT [10]. Furthermore, mitochondria-targeted zirconia (ZrO_2) composite nanoparticles (MZCNs) have been used for the treatment of hepatocellular carcinoma under microwave irradiation [10].

3. Conclusion

Based on the summary and analysis of research literature above, scholars currently focus on drug therapy and immunotherapy for the treatment of liver cancer. Significant research results have been achieved in these fields, such as the clinical use of sorafenib. In addition, more in-depth studies have been conducted on oncolytic virus therapy. The study of liver cancer therapy employs multi-disciplinary and multi-mode treatment methods to address issues related to safety, innovation, and inhibition ability. However, it is important to acknowledge that certain problems still need to be addressed, such as the insufficient HLA Class I and Class II libraries displaying TAA-specific T cell epitopes in immunotherapy, more research is needed to understand the mechanism of T cell failure. In oncolytic virus therapy, optimizing systemic viral delivery in immunotherapy and enhancing cross-priming of viral transmission and anti-cancer immunity within tumours are still unresolved issues. The research conducted by scholars on the principles of action, drug effects, and clinical outcomes has provided a rich theoretical basis and practical experience for the treatment of liver cancer.

Numerous case studies have also been conducted on different cases. In the future, by developing more safer, more efficient treatment and medicines, it may be possible to enhance the overall survival of HCC patients.

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