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Advances in the Treatment of Primary Liver Cancer

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Abstract

Primary liver cancer (PLC) is one of the common malignant tumors. With high incidence and poor prognosis, PLC has become one of the major diseases which is seriously harmful to human life and health. In recent years, the research work have been summarized on the status of the treatment of primary liver cancer, and great progress has been made, especially the significant progress in the early diagnosis, surgical treatment, and comprehensive treatment of liver cancer made to improve the quality of life of patients. In spite of many methods can be used to improve the quality of life, there are still issues need to be studied deeply. The overview of the progress in the therapy research of liver cancer had been done in this paper that may provide assistance for the further treatment of such disease.

Keywords: Primary liver cancer; Diagnosis; Treatment; Progress; Status

Introduction

Primary liver cancer is one of the most common malignancies in the world, and currently surgery is still considered to be the most effective and curative treatment. However many patients have lost the chance of surgical treatment when the first time of treatment is near, and the recurrence rate of surgery after 5 years is also higher. Thus, the non-surgical treatment in the medical profession has received considerable attention. Great progresses in a lot of non-surgical treatments have been made in recent years. In this paper, the status of the treatment of primary liver cancer is reviewed.

Advances in non-surgical treatment of primary liver cancer

Non-surgical treatment plays an important role in the treatment of primary liver cancer. Non-surgical treatment of primary liver cancer includes trans catheter arterial chemoembolization, percutaneous ablation therapy, radiation therapy, chemothep, etc.

Percutaneous ablation therapy

Percutaneous ablation is a curable treatment options for small tumors. It can be used for the treatment of HCC tumors which diameter is less than 5 cm. Tumor recurrences and survival rate after ablation is almost the same to surgical resection for the tumor which diameter is not more than 2 cm [1-3]. Typically, percutaneous ablation is conducted by injecting chemicals into the tumor under ultrasound guidance, and extreme temperatures can also be used to destroy tumors.

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Percutaneous ethanol injection tumor (PEIT) is another percutaneous ablation therapy method. The coagulation of ethanol protein and thrombosis microvascular caused by ethanol protein is the therapeutic mechanism of PEIT. With lower treatment costs and fewer complications, 90-100% efficiency can be reached by PEIT when the cancer treatment in which the diameter of tumor is lower than 2 cm [1]. PEIT also has a significant character on shrinking tumor lesions, controlling and delaying of the growth in tumor. Experiments [4] made by Omata et al. showed that the 5-year survival rate could reach 64.7% for the patients in which the tumor diameter is not more than 3cm and the number of tumors is less than 3. However, the PEIT efficacy in elderly patients [5] is poor relatively (3 and 5 year survival rates were 83%, 52% and 27% respectively).

Combined with TACE, the effect of PEIT can be improved. TACE-induced avascular necrosis of the tumor destroyed the fiber spacing inside the tumor, which contribute to the dispersion of ethanol, and the reduction of residual tumor after treatment [6-7].

For the tumor which diameter is more than 2cm, Radio frequency ablation (RFA) is more effective than PEIT, it can kill tumor cells by generating heat conducted by electrode alternating current [8-9].

RFA treatment resulted in complete tumor destruction which is difficult to destroy the tumors close to large vessels, subcapsular or the gallbladder, and orthotopic recurrence rate of tumor is higher. So the insufficiency of RFA can be avoided by binding to PEIT, and result in complete tumor destruction. The radiofrequency treatment on the tumor located in the first hilar should be careful, so as not to damage the bile duct. Uehara et al. [10] reported that the damage could be reduced by the formation of ascites to increase the gap between the diaphragm and the abdominal wall.

Because of the similar indications in RFA and PEIT, Seror et al. [11] compared the difference of efficacy between RFA and PEIT, and found that 2-year total survival rates were 91.2% and 70.8%, tumor-free survival rate was 80.7% and 68.5%, the complication rate was 15% and 6.9% respectively. Other researches [12] also demonstrated that the efficacy of RFA is superior to laser treatment.

The thermal effects of microwave can induce coagulation necrosis of the tumor. Microwave coagulation therapy for small hepatocellular carcinoma can get an ideal effect. The time in each treatment is shorter, and the treatment is also more frequent compared with RFA [13]. For the tumor which diameter is more than 3 cm, can be treated by a multi-point needle and a combination of ways to improve the efficacy of radiation. For small tumors near the surface of the liver, Seki et al. [14] presented that microwave treatment can be carried out with laparoscopic, and they summarized small hepatocellular carcinoma data among 68 patients. The results indicated that, 3 and 5-year survival rates were 97%, 81% and 43% respectively and incidence of complications is lower.

The temperature of superconducting tip can be reduced to 140e in a few minutes when the release of argon gas which is in high pressure and normal temperature. With the release of helium, the temperature can be generated 45e. Argon-helium refrigeration has higher efficiency and more reliable efficacy compared with the traditional frozen in liquid nitrogen.

Other percutaneous ablations include percutaneous laser hyperthermia in the tumor and high-intensity focused ultrasound. Multi-point fiber laser treatment can be extended freezing range under ultrasound guidance. Hyperthermia also has a hemostatic effect and can stimulate the body's immune function, promote the body to kill tumor. However, reports currently showed that multiple laser hyperthermia was used in the multiple primary liver cancer treatment in which the tumor diameter is shorter than 2 cm. High intensity ultrasound therapy focused on the tumor in the liver, produce heat directly to kill tumor cells owing to the short wave length of high-intensity ultrasound and its easiness to penetrate tissue. However, because of the small high-intensity focused ultrasound area, repeated several times to operate in the treatment of tumors, and the ribs and

hollow organs of the ultrasound generated by absorption and reflection effects, the applications of the high-intensity focused ultrasound therapy was limited.

Embolization therapy

Trans catheter arterial chemoembolization (TACE) is considered to be the preferred method of non-surgical treatment of primary liver cancer after the reports by Goldstein et al. [15]. The definition of TACE indications made by Chinese Society of Surgery Liver Surgery Group is as followed:

(1) Liver function belong to class A or B;

(2) Cannot be treated with surgery;

(3) Tumor recurrence after hepatectomy.

In principle, interventional radiology treatment before surgery in resectable liver cancer does not need to be conducted. After repeated TACE (usually 2-4 times) treatment, tumor in some patients can be significantly reduced for the inoperable treatment of liver cancer patients, especially on the right lobe of the main or multiple lesions, which also seized the chance to the radical surgery. But possible liver atrophy, severe decompensated liver function and other complications also need to be avoided. Vogl et al. [16] reported that TACE could be used for primary liver resection preventive treatment to remove probable residual postoperative liver tumor cells, it also was adapted to the portal vein which did not occur fully thrombosis; tumor volume did not exceed 70% of the whole liver. TACE is an important complement to liver cancer resection, it is also as an effective measure to be part of the second phase of surgery in patients with liver cancer. But because of poor efficacy on the distant metastases of multiple satellite lesions, it can not achieve satisfactory results of clinical treatment. Therefore a comprehensive treatment of TACE combined with surgical resection, biological therapy, Chinese medicine, etc. can be conducted to eliminate tumor cells, and prolong survival, reduce the relapse rate further to achieve the purpose of long-term prevention or cure.

Radiotherapy and chemotherapy

The current mainstream of liver cancer radiotherapy is three-dimensional conformal radiotherapy. Normal tissue complication probability (NTCP), tumor control probability (TCP) cannot be taken into account in regular radiotherapy. Three-dimensional conformal radiotherapy can take the account of TCP and NTCP into better, improve safety target radiation dose, and the maximum can be increased to 90 Gy. Data [17] showed that three-dimensional conformal radiation therapy could improve the median survival of liver cancer patients with inoperable interventional treatment.

For patients can be treated with surgery, surgical treatment should be preferred. However, in clinical work, 80% of primary liver cancer already exists in intrahepatic distant metastasis or with severe cirrhosis of the liver when diagnosed. At this time, systemic chemotherapy, including non-surgical therapy can improve the quality of life of patients or prolong survival. However the side effects in systemic chemotherapy, the result is not satisfactory. The clinical application is limited to local chemotherapy, including trans catheter arterial chemoembolization (TACE), surgical hepatic artery catheter (HAI) and/or portal vein catheterization (PVI) chemotherapy, intraperitoneal chemotherapy. And single-agent chemotherapy, including anthracycline antitumor drugs, fluorouracil, camptothecin, cisplatin gemcitabine, etc., the effect is also not good, now even generally do not be advocated as a separate application. Currently chemotherapy regimens such as joint programs with ADM (E-ADM) and/or PDD-based; E-ADM, PDD and 5-ECF program consisting FU; L-OHP-based joint program such as XELOX regimen [18] and GDMOX program [19] are used widely.

Advances in surgical treatment of primary liver cancer

So far, there are several recognized surgical resections of liver, such as partial resection of hepatic resection, liver transplantation and other methods. They are mainly used for the removal of the tumor that diameter less than 3 cm in small liver disease, it is also very effective treatment to extend the life span of patients. In recent years, the number of successful removal of the tumor which diameter is beyond 5 cm is increasing. Because of liver function and liver capacity of large hepatocellular carcinoma was significantly more worse than that of small hepatocellular carcinoma, there is a certain degree of difficulty and danger of surgery. The difficulty and danger of such large HCC are getting lower and lower with the development of surgical techniques. The treatment effect is also more satisfying. There are many success cases from diameter 10-15 cm in stage resection large liver cancer. Such surgery significantly reduces mortality, and also avoids complications effectively. But in stage I, some huge hepatocellular is unrespectable, so the catheter can be used in preoperative embolization of the hepatic artery, hepatic artery ligation, refrigeration and other surgical means comprehensively to shrink the tumor after resection in stage II. Survival rates of resection after narrowing and ablation of small hepatocellular carcinoma was similar. For hepatocellular carcinoma with venous thrombosis, patients can be resected with surgery plus integrated approach to portal vein thrombectomy after trans catheter arterial chemoembolization or intraoperative portal vein and hepatic artery catheter tube etc., this treatment is promising for prolonging survival period.

Advances in interventional treatment of primary liver cancer

Interventional therapy need certain specific carrier (including ferritin antibodies, alpha-fetoprotein antibodies, anti-human hepatocellular carcinoma antibody, anti-hepatitis B surface antigen and non-iodized oil etc.), the drugs (such as epirubicin or biological response modifiers), or other anti-tumor substances (such as radionuclides) which were selectively delivered to the tumor site, in order to improve the therapeutic effect of the treatment method. Intervention methods (adopted by the hepatic artery) have their great advantages, can reduce or avoid three major issues of biological immunotherapy, namely dilution, physical barriers and non-specific conductivity absorption. It can increase local drug concentration, improve cancer/liver ratio and reduce systemic toxicity. Radionuclides, such as 131 I, is greater than chemotherapy, and the use of dual-warhead can combine advantage of chemotherapy and radiation therapy to further improve the anti-tumor efficacy. A variety application of mixed monoclonal antibodies and the reduced antigen expression with isotope heterogeneity warheads can increase the local concentration of subclinical lesions, reduce tumor recurrence and metastasis.

Radiological techniques developed by interventional gene therapy have become the prototype of the line and is moving toward the clinic. In the guidance of percutaneous, target genes are directly into the local tumor reliablly and simply. Tumor cells were transfected totally. While injected via the hepatic artery, the gene can be expressed in the target organ to enhancing the therapeutic effect and tumor sensitivity, minimizing its side effects [20]. Joint intervention by the way of gene therapy, many ways can adjust the body's anti-tumor effect. A comprehensive strengthening of various therapeutic effect of a single gene, which includes suicide gene combination therapy (such as CD/5-FC and HSV-tk/GCV system). Drozdzik et al. [21] observed the effect of the combined therapy of IL-12 gene and HSV-tk gene in rat liver cancer model, its efficacy was significantly better than that with IL-12 gene or HSV-tk gene alone. Genes involved in the future combination therapy include:

(1) Choose a more effective target gene and combine with others, apply them on different aspects of cancer treatment;

(2) Combine the TACE and cytokine gene therapy, use most commonly "sandwich" method, and prepare joint cytokine genes with chemotherapy drugs, gene therapy and try to use a special emboli;

(3) Try to conduct postoperative indwelling vascular chemotherapy pump continued to import and so on.

Through close cooperation with radiologists and molecular biology, interventional gene therapy will be more mature in clinic.

Advances in Immunotherapy of Primary Liver Cancer

Active immunotherapy

There may be different antigen components between tumor cells and normal cells which induce anti-tumor immune response and then take the initiative to kill tumor cells during the active immunotherapy of tumors. The anti-tumor immune sensitivity is often low, can only detect the immunogenicity of the antigens of tumor surface, can not induce tumor-specific immune response. Meanwhile, the method needs to rely on the host immune function to ensure that the vaccine can stimulate the host immune generating anti-tumor immune response. Currently clinically active immunization of liver cancer, includes hepatocellular cancer which mainly consists of vaccines, recombinant vaccines and dendritic cell-fetoprotein (dendritic cell, DC) vaccine.

Yang et al. [22] injected autologous whole tumor cell vaccine to induce specific immune response in a mouse model of HCC H22 and demonstrated a significantly longer survival time. Kuang et al. [23] conducted a randomized controlled phase II clinical trials, the granulocyte-monocyte colony stimulating factor (granulocyte-macrophage colony-stimulating factor, GM-CSF), interleukin-2 (interleukin-2, IL-2) combined with autologous formalin-fixed tumor tissue was applied among liver cancer patients. The treatment group 2-year survival (18/19) was significantly higher (13/21), overall survival was significantly improved (P=0.01). Peng et al. [24] investigated 67 cases of hepatocellular carcinoma patients after randomized controlled study with an average follow-up of 33.6 months. It showed that, 2, 3-year recurrence rate of liver cancer patients after tumor vaccine treatment was 12.6%, 35.9% and 54.0% respectively, which was significantly lower than the control group (after operation, , 2, 3-year recurrence rate was 31.6%, 61.3%, 72.1% respectively).

Butterfield et al. [25] reported the application of four recombinant alpha-fetoprotein (AFP) vaccine in clinical trials of immunotherapy IV peptide epitopes of primary liver cancer, the results showed that AFP peptide epitopes in these patients with liver cancer in high concentrations of serum AFP may trigger antigen-specific T cell immune response, but not observed in clinical response, the emergence of AFP is also not reduced. Further studies showed that the application of autologous DC transduced cells of 10 patients about AFP polypeptide treatment on III/IV stage liver cancer. 6 patients showed increased AFP epitope-specific T cells and IFN-γ secretion, suggesting AFPs vaccine immune activity [26].

Tatsumi et al. [27] used α-galactose nerve amide pulsed DC, and injected therapy on CMS4 hepatocellular liver tumor-bearing mice directly. The results showed complete tumor regression in tumor-bearing mice and prolonged survival. 14 patients were achieved a partial response and 17 patients achieved clinically stable, one-year survival rate was significantly improved after Lee et al. [28] used autologous tumor lysate pulsed DC after intravenous treatment Ⅳ among 31 cases of liver cancer. In 35 patients, Palmer et al. [29] used that is not suitable for surgery or injections topical treatment of liver cancer cell lysis objects outside sensitized mature autologous DC vaccine, found four cases in 17 patients that have decreased to 30% below the initial value and 1 case to 10% in which baseline AFP is higher than 1000 μg/L. It was proved that the treatment of liver cancer with autologous DC was safe and effective. Nakamoto et al. [30] investigated the injection effect of streptococcal vaccine-derived DC antitumor immunotherapeutic agent OK432 on 13 cases in liver cancer patients after transcatheter arterial embolization. The results showed its recurrence-free survival compared with control groups.

Passive immunotherapy

Passive immunotherapy of tumors is to activate the body's immune response depend on exogenous substances, including various types of antibodies and immune effector cells, such as lymphokine-activated killer cells (LAK), cytokine-induced killer cells (CIK), tumor infiltrating lymphocytes (TIL), tumor antigen-specific cytotoxic T cells (CTL), etc. Adoptive immunotherapy is the hot spot in HCC passive immunotherapy which receive more attention. The product has specific immunity sensitized lymphocytes, which are delivered to the body of HCC patients to get anti-tumor immunity.

Bertelli et al. [31] investigated 31 cases of liver cancer patients which treated with injecting IL-2-activated autologous peripheral blood LAK for 1 month and not by surgery therapy, the results showed that LAK therapy can significantly prolong the survival period. For patient the acceptance is 12 treatment and more, its efficacy is better, but radiographic examination showed no significantly reduced tumor size.

Hui et al. [32] found that liver cancer CIK treatment after radical treatment can significantly improve disease-free survival, but the improvement is not obvious in overall survival. TIL comes from tumor infiltrating lymphocytes. IL-2 requires a low concentration of anti-tumor activity and high specificity in vitro amplification. However, there is a risk of tumor cells TIL reinfusion currently rarely used in clinic.

Non-specific immunotherapy

For most immunogenic tumor, specific immune response is strong but hepatocellular tumors are immunogenic weak, which is due to the continuous insufficient increase of tumor antigen expression which can cause an effective immune response. One study found there was a presence of severe immune suppression [33], which may be related to the imbalance of T cell subsets in patients with hepatocellular carcinoma, leading to the specific performance that CD3 and CD4 cells decreased, CD8 cells increased which resulted in, an increased CD4/CD8 ratio and activity of natural killer cells (NK) decreased.

Cheng et al. [34] investigated 57 cases of liver cancer patients after chemotherapy combined with hepatic artery embolization (TACE) and thymosin α1 therapy, found that thymosin preparations may delay tumor recurrence and prolong survival time for nearly two months. And survival time significantly prolong and improve the quality.

Shuqun et al. [35] found that the combination treatment with lamivudine and thymosin α1 in chronic hepatitis B patients with primary hepatocellular carcinoma, HBV replication status in the postoperative combination may delay tumor recurrence and prolong survival time. However, the mechanism is unclear, probably by inhibiting replication of hepatitis virus to achieve the indirect effect of delaying the recurrence of liver cancer.

Sangro et al. [36] used injection treatment with an adenoviral vector encoding IL-12 in 8 cases of liver cancer patient. One had a partial response, six cases kept stable disease. And another case of disease had progression, it showed the anti-tumor effect of IL-12.

Tomova et al. [37] found that low doses of IL-2 can reduce the viral hepatitis B or hepatitis C in patient's body. Palmieri et al. [38] used low-dose IL-2 (1MIU/d) to treat 18 patients with advanced unresectable HCC patients, and the degrees of disease of 17 patients was controlled, including one case for prolong survival to 46 months.

Lo et al. [39] found that intramuscular injection of IFN-α, after surgical resection of hepatitis B, can significantly improve the 5-year survival in stage III/IV patients, but failed in Phase I/II patients despite higher five years survival (both are higher than 90%) and delayed relapse. Mazzaferro et al. [40] tested 150 cases of hepatitis C hepatocellular carcinoma patients after the injection of IFN-α therapy with randomized controlled studies, the result was shown that tumor-free survival and overall survival was not different. In addition, HCC in cirrhotic basis may not tolerate IFN-α therapy.

Liver cancer immunotherapy is the new direction of current research, improving the quality of life for patients with liver cancer and prolong survival time, reduce the relapse rate. Until now, a variety of immune therapies and immunomodulatory strategies have shown resistance to liver cancer and preliminary clinical efficacy of biological immune activity in HCC patients. With the development of molecular biology; molecular immunology penetration and immune gene therapy, it will provide more new ideas for liver cancer immunotherapy. Development and improvement of new vaccines and immunomodulators is expected to further improve immunotherapy sensitivity and specificity, to play a more important role in clinical practice.

Advances in the biological treatment of primary liver cancer

Dr. Olidham from United States proposed a new concept of cancer biotherapy in the 1980s. Together with primary liver cancer surgery, radiation therapy, adjuvant therapy, it has become the fourth main therapy mode, which is to enhance the body's defenses against tumors by regulating the body's own biological responses, thereby inhibiting and (or) delaying tumor growth and improving survival, reducing the relapse rate and improving the quality of life. Currently only a small part of the biological treatment method or technology has been used in clinical practice, and most still in development and clinical trial stage [41].

Surgical resection is the preferred method of liver cancer therapy. for the most advanced unresectable hepatocellular carcinoma patients, the application of a variety of methods such as TACE, PEI, RFA, hyperthermia, radiation therapy, Chinese medicine comprehensive, sequential therapy is still the most effective measures. Comprehensive treatment which is widely used in clinic already achieved desired results, effectively improved the quality of life of patients and significantly extended the survival time. However, due to the particularity of the individual, how to choose and how to achieve the best results from a variety of treatment methods become a problem to be solved. Further exploring new and effective treatment, and gradually improving the standardization of the comprehensive treatment of liver cancer will become one of the important clinic research directions. With the development of molecular biology and other related disciplines, further research on liver cancer oncogenes, tumor suppressor genes, molecular genetic mechanisms of HCC recurrence; metastasis of HCC tumor-specific immunotherapy and gene therapy will become an important research issue. It is believed that with the progress of science and technology and people's awareness of the disease in depth, the better, newer, more effective treatments to PLC will be found in the future.

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