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THE IMMUNOTHERAPY OF HEPATOCELLULAR CARCINOMA

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Abstract:-
Primary liver cancer is one of the most common malignancies in the world, and surgery-based combined therapy is still being the dominant treatment option. Though surgery is considered to be one of the most effective and curative treatments, many patients have lost their chances of surgical cure as they are in advanced stage of the disease when diagnosed. Thus, the non-surgical treatment in the medical profession has received considerable attention, because 5-year recurrence rate after surgery is also high. In recent years, good progresses have been made in many non-surgical treatments. In this paper, the treatment status of primary liver cancer will be reviewed.

Keywords:- *Primary liver cancer; Immunotherapy; Treatment progress*

Why Use Immunotherapy for HCC Patients?

The success of immune checkpoint blockade with anti-cytotoxic T lymphocyte associated antigen 4 (CTLA-4) antibodies in advanced melanoma patients has brought renewed hope for immunotherapy in cancer. In addition, immunotherapy is particularly attractive for HCC for several reasons. HCC is typically an inflammation-associated cancer and can be immunogenic. Indeed, cases of spontaneous regression of HCC have been reported and many of these cases were related to systemic inflammatory responses. [01] In addition, the majority of HCC patients suffer from cirrhosis of viral etiology, alcoholism, or nonalcoholic steatohepatitis. Since immunotherapeutic drugs are not metabolized in the liver, they may have predictable pharmacokinetic profiles in cirrhosis patients. Indeed, preliminary clinical data with antibody-based therapy has not shown any severe hepatoxicity. [02] Nevertheless, the successful application of immunotherapy in HCC will have to take into account the liver cancer-specific immune microenvironment and responses.

1. Active immunotherapy

Hepatocellular carcinoma (HCC) accounts for 95%17 (IL-17) promote angiogenesis of HCC and recruit neutrophils to enhance angiogenesis [03]. The effector function of CD8+ T cells is prone to be impaired by increased Tregs, which predicts a poor prognosis of HCC patients. In addition, the functional impairment of other cells like natural killer (NK) cells also contributes to tumor progression , Allogenic γδT cells could be developed into a very promising 'immune drug' for malignant tumor therapy. [04].Tumor cells and normal cells may exist in different antigen components, active immunotherapy of tumors is to use these antigen components to induce anti-tumor immune response, and then take the initiative to kill tumor cells. HCC typically occurs in the setting of chronic inflammation such as viral hepatitis. While patients with early disease have a relatively good prognosis with a 5-year survival of more than 70%, the majority of patients with HCC are diagnosed with late stage disease resulting in an overall 5-year survival rate of less than 16% [05]. Impaired metabolism due to liver cirrhosis limits the use of cytotoxic chemotherapy and a number of studies indicate intrinsic resistance of tumor cells to commonly used chemotherapeutic reagents in HCC [06]. A point worth noting is that the anti-tumor immune sensitivity is often low, only detectable immunogenicity of the tumor surface antigens do not induce tumor-specific immune response and these antigens are not enough to reject the tumor and are relatively weak antigens . Meanwhile, the method needs to rely on the host immune functions to ensure that the vaccine can stimulate the host immune system to generate anti-tumor immune response. Spontaneous immune responses including T-cell responses [07] as well as humoral responses to different tumor-associated antigens have been described in HCC. Currently, clinically active immunization of liver cancer includes hepatocellular cancer vaccines, recombinant vaccines and dendritic cell-fetoprotein (dendritic cell, DC) vaccine. Yang et al [08] found that in a mouse model of HCC H22 injection of autologous whole tumor cell vaccine to induce specific immune response demonstrated significantly longer survival time. Several characteristics relating to both the treatment and biology of HCC make it amenable to immunotherapy. However, while previous clinical trials have focused on the feasibility and safety of immunotherapy for patients with advanced HCC, non-randomized Phase I or II studies have yet to demonstrate the efficacy of immunotherapy for this disease [09]. Kuang et al conducted a randomized controlled phase 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 for liver cancer patients in the treatment group ,2-year survival (18/19) was significantly higher (13/21) , overall survival was significantly improved (P = 0.01). Peng et al concluded from 67 cases of hepatocellular carcinoma patients after randomized controlled study, with an average follow-up of 33.6 months showed that liver cancer patients after tumor vaccine treatment groups 1, 2, 3-year recurrence rate were respectively 12.6%, 35.9%, 54.0%, significantly lower than the control group (after 1, 2, 3-year recurrence rate was 31.6%, 61.3%, 72.1% respectively). Butterfield et al reported the use of a vaccine four recombinant alpha-fetoprotein (AFP) in clinical trials of immunotherapy peptide epitopes of primary liver cancer, showed 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, also the emergence of AFP is not reduced. Further studies showed that the application of autologous DC transduced cells of 10 patients AFP polypeptide IV stage liver cancer, 6 patients appear AFP epitope-specific T cells increased and IFN-γ secretion, suggesting AFP vaccine immune activity. Tatsumi et al used α-galactose nerve amide pulsed DC, and direct injection therapy CMS4 in hepatocellular liver tumor-bearing mice, the results showed: complete tumor regression in tumor-bearing mice, prolonged survival. Lee et al using autologous tumor lysate pulsed DC after intravenous treatment 31 cases of liver cancer and 14 patients achieved a partial response and 17 patients achieved clinically stable, one-year survival rate was significantly improved in 35 patients . Palmer et al with advanced liver cancer patients who were not suitable for surgery or injections topical treatment of liver cancer cell lysis mature autologous DC vaccine, 28% of the patients and controls improved imaging on 17 patients at baseline AFP elevated> 1000μg patient / L in four cases have decreased to 30% below the initial value, and 1 to 10%, and proved to be safe and effective in the treatment of liver cancer with autologous DC. Nakamoto et al [10] researched liver cancer patients after Tran's catheter arterial embolization in 13 cases after injection of streptococcal vaccine-derived DC antitumor immunotherapeutic agent OK432 stimulated, the results show its recurrence-free survival compared with control groups.

The immune response engaged by a specific antigen and its subsequent intensity is regulated not only by major histocompatibility receptors, but also by co-stimulatory and co-inhibitory molecules that modulate response based on the physiological context. Immune checkpoints function as an extensive inhibitory program that is crucial for maintaining self-tolerance and modulating the duration and extent of physiological immune responses in peripheral tissues, ultimately helping to minimize extra tissue damage. Several immune checkpoint pathways have been shown to be exploited by tumors so as to aid in avoidance of immunosurveillance, particularly involving the T cell responses that are specific for

tumor antigens. Many immune checkpoint molecules, such as the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and PD-L1, have been detected in the tumor microenvironment, and are often overexpressed as well [11-13] .Tumor-associated antigen (TAA)-specific T cell responses have also been detected in peripheral blood following RFA [14]

2. Passive Immunotherapy

Passive immunotherapy of tumors is to give the body's immune response infusion of exogenous substances, including various types of antibodies and immune effector cells, such as lymphokine-activated killer cells (LAK), cytokine-induced killer cells (CIK). Bertelli et al did researches on 31 cases of liver cancer patients who have not undergone surgical treatment, injected with IL-2-activated autologous peripheral blood LAK therapy, treatment for 1 month, showed LAK therapy can significantly prolong the survival period of 12 patient, its efficacy is better, but radiographic examination showed no significant shrink in tumor size. Hui et al [15] found that liver cancer after radical I CIK treatment can significantly improve disease-free survival, but the effect is not obvious in improvement of overall survival. TIL from tumor infiltrating lymphocytes, in vitro amplification of IL-2 requires a low concentration of anti-tumor activity and high specificity. However, there is a risk of tumor cells TIL reinfusion currently rarely used clinically.

3. Non-specific immunotherapy

For most immunogenic tumor, specific immune response is effective but hepatocellular tumors are weakly immunogenic, which is due to the continuous growth of tumor Antigen expression is insufficient to cause an effective immune response. The study found that the presence of severe immune suppression may be related to imbalance of T cell subsets in patients with hepatocellular carcinoma and the specific performance of CD3 and CD4 cells decrease, an increase in CD8 cells, CD4/CD8 ratio decreased natural killer cells (NK) cell activity. Cheng et al did researches on 57 cases of liver cancer patients. After chemotherapy they received hepatic artery embolization (TACE) and thymosin α1 therapy simultaneously and found that thymosin preparations may delay tumor recurrence and prolong survival time. The relapse time of treatment group has delayed nearly two months, survival time has been significantly prolonged and the quality of life has also been improved. They also found the radical resection could have better efficacy with hepatitis cirrhosis. Studies have shown that, in addition to immune stimulating effects, thymosin α1 also have direct antiviral and anti-tumor effects. Shuqun et al found that chronic hepatitis B patients with primary hepatocellular carcinoma and HBV replication status in the postoperative combination with lamivudine and thymosin α1 may delay tumor recurrence and prolong survival time.. Sangro et al used an adenoviral vector encoding IL-12 in tumor injection therapy eight cases of liver cancer; one had a partial response, six cases of stable disease, one case of disease progression, showing the anti-tumor effect of IL-12. Tomova et al [16] found that low doses of IL-2 can reduce the viral hepatitis B or hepatitis C copies in patient's body. Palmieri et al used low-dose IL-2 (1MIU / d) for 18 patients with advanced unresectable HCC patients, and 17 patients subjected to varying degrees of disease control, including one case of survival of 46 months. Lo et al found that after surgical resection of hepatitis B and intramuscular injection of IFN-α, in stage III / IV patients can significantly improve the 5-year survival, and in Phase I / II patients failed to improve despite five years survival (both> 90%), but can delay relapse. But Mazzaferro et al tested on 150 cases of hepatitis C hepatocellular carcinoma patients after injection of IFN-α therapy randomized controlled studies have shown that tumor-free survival and overall survival were 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 is significant. Currently, 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 and molecular immunology penetration and subsequent development of immune gene therapy, will provide more new ideas for liver cancer immunotherapy such as development and improvement of new vaccines and immunomodulators, which is expected to further improve immunotherapy sensitivity and specificity, to play a more important role in clinical practice.

Inhibitory molecules

One mechanism of escape includes overexpression or decreased expression of cell death related molecules, such as Fas/FasL, PD-1/PD-L1, CTLA-4, and Decoy receptor 3. Fas is a cell-surface protein that belongs to the family of tumor necrosis factor (TNF) receptors [17]. The other mechanism involves the escape of excessive cell death related molecules or reduces the expression, such as Fas/FasL, PD-1/PD-L1, CTLA-4 and Decoy Receptor 3. Fas is a cell surface protein that belongs to the tumor necrosis factor (TNF) receptor family. Fas ligand (FasL) is a type II membrane protein that binds to Fas [18]. Cross-linking of Fas with FasL induces apoptosis of Fas-bearing cells. FasL is found in immune-privileged sites, such as the testis and eye [19,20]. HCC tissues have been reported to express Fas weakly and at low frequency [21]. Additionally, elevated soluble Fas (sFas) levels in HCC patients have been reported [22]. Loss of cell-surface Fas in HCC and neutralization of FasL by sFas might be involved in tumor cell immune escape [23]. PD-L1 is member of the B7 family that can interact with programmed death-1 (PD-1). Its receptor, PD-1, is expressed on activated T and B cells and elicits inhibitory signals [24]. PD-L1 is expressed on dendritic cells, macrophages and parenchymal cells and various cells of human cancer. [25]. In HCC, PD-1 expression is upregulated on effector-phase CD8+ T cells, especially in tumor-infiltrating CD8+ T cells [26]. High expression of PD-1 on T cells both in TILs and peripheral blood mononuclear cells (PBMCs) is correlated with a poor prognosis in HCC patients after surgical resection [27]. Additionally, D-L1 expression on Kupffer cells (KC) has been shown to increase in tumor tissues in patients with HCC, and is correlated with poor survival [28]. Those above suggest that effector phase T-cell inhibition is associated with tumor survival. Decoy

receptor 3 (DcR3), a member of the TNF receptor superfamily, might also be involved in immune escape. DcR3 inhibits FasL-induced apoptosis by binding to its ligand Fas. Additionally, DcR3 overexpression in HCC has been reported [29,30].

Conclusion

Among all kinds of cancers, liver cancer is a malignant disease that is difficult to treat with short survived time and high mortality. Improvement in the efficacy of liver cancer treatment relies on improvement of basic and clinical researches, which include further understanding the onset and development of liver cancer, individual and environmental factors, mechanism of action, mechanism of metastasis and recurrence after surgical resection of liver cancer as well as signaling mechanism such as specific antigen and genes etc. However, the available data indicates that immunotherapy has the potential to improve survival without impairing the quality of life, and is expected to be effective for prevention of recurrence. Immunotherapy for HCC is still in the preclinical and clinical trial phases of development; however, it will become available and be clinically successful in the near future. Analysis of the correlation between clinical and immunological responses is required to demonstrating the efficacy of immunotherapy. The challenge remains to be the design of clinical trials to appropriately evaluate novel immunotherapies or combination therapies, and to allow feedback to facilitate ongoing development.

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