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Novel therapeutic strategies for treatment of liver cancer

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Abstract

Liver cancer is the most common type of solid tumor with poor prognosis. Various environmental, genetic and epigenetic factors including aberrant molecular signaling pathways play a significant role in pathogenesis of liver cancer. Targeting these molecular pathways has paved the way for evolution of molecular targeted drugs. Liver being less immunogenic strategies to improve immunosurveillance evasion by cancer cells has been addressed using immunotherapy. Research on novel therapeutic strategies such as immunotherapy, molecular targeted therapy, gene therapy is ongoing. This review aims to discuss current trends and recent developments in the field of liver cancer therapy.

Keywords: liver cancer, immunotherapy, targeted therapy.

1. Introduction

Liver cancer is heterogenous cancer with high incidence and mortality. It is the third leading cause of cancer-related deaths worldwide and develops as a consequence of end-stage liver disease. The etiology of liver cancer includes infection with hepatitis B and C viruses, aflatoxin B, tobacco, vinyl chloride, and heavy alcohol intake, and non-alcoholic fatty liver disease hemochromatosis, Schistosoma japoricum infection along with hepatitis virus infection, cirrhosis due to alpha-1 antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. The pre-neoplastic stage of liver cancer exhibits gross genomic alterations which promotes repetitive cycles of cell death and compensatory hepatocellular proliferation. This noxious milieu deregulates many molecular signaling pathways culminating in liver cancer. [1,2]

Liver exhibits immune tolerance since it is continuously exposed to foreign molecules such as food and gut flora. Also multiple immune suppressive mechanism are synchronized by the cancer cells itself namely, down regulation of MHC protein and co-stimulatory molecules such as B7-1 and B7-2, up-regulation of immunosuppressive cell population such as regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSC), impairment of dentritic cells function. Other mechanisms include up-regulation of immunosuppressive cytokines such as IL-10 and transforming growth factor (TGF-β) and immune checkpoint molecules such as PD-1.[3,4]

Liver cancer is one of the most common solid tumor malignancies, and is mostly diagnosed in intermediate to advanced stage and hence palliative therapy is the only cure. Surgery, non-surgical invasive techniques, chemotherapy, radiotherapy and liver transplantation are the mainstay treatments for liver cancer. But being less immunogenic, highly resistant to chemotherapy, defiant to radiotherapy and scarcity of organ donors makes liver transplantation less feasible, development of novel therapeutic agents is the need of the hour and this review focuses on the current trends of novel cancer therapeutics. [5]

2. Molecule targeted drugs

Targeting angiogenesis, growth factors, protein kinases, (TGF)-β, hepatocyte growth factor (HGF)/c-MET, fibroblast growth factor (FGF) and Notch signaling pathways are promising new avenues of molecular targets for therapeutic intervention in liver cancer. Though some of these drugs are used for treating other cancer types its use in liver cancer is being extensively investigated in clinical trials as mainstay or adjuvant therapy in liver cancer.

2.1 VEGF inhibitors

Vascular endothelial growth factor (VEGF) mediates angiogenesis in liver cancer and blocking VEGF-mediated pathways either by anti-VEGF neutralizing antibody such as bevacizumab or tyrosine kinase inhibitors such as sunitinib, sorafenib, bivranib, vatalanib, cediranib are being assessed in liver cancer patients. [2,6] Clinical trial studies on bevacizumab showed good anti-tumor activity and also increased median survival rate. Sunitinib in clinical trials improve overall survival rate but death due to bleeding was reported. [8]

2.2 MAPK inhibitors

Mitogen activated protein kinase (MAPK) consist of kinase cascade that is regulated by phosphorylation and de-phosphorylation by specific kinases, phosphatases, and GTP/GDP exchange proteins. Clinical trials using MAPK blockers such as sorafenib, selumetinib, lenvatinib, apatinib and regorafenib is ongoing.[6] Based on the SHARP clinical trial sorafenib has been approved for treatment of patients with advance hepatocellular carcinoma. It increases the overall survival rate and time of progression of disease. [2,7] It blocks signal transduction mediated by Raf/Ras/MEK/ERK pathway and inhibit various tyrosine kinases. The adverse effects are diarrhoea, fatigue, weight loss and hand foot skin reaction. Regorafenib is a sorafenib derivative with activity against multiple kinases. Clinical trial studies in 86 liver cancer patients improved overall survival rate and most of patient achieved disease stabilization. [2,8] Trametinib and refametinib are MEK inhibitors, a protein acting downstream of the Ras pathway and its inhibition can disrupt cancer cell growth and survival.

2.3 EGFR inhibitors

Epidermal growth factor receptor (EGFR) pathway on activation triggers a number of downstream signaling pathways such as PI3K/Akt/mTOR and the Ras/Raf/ MEK/ERK pathways. The receptor most studied in liver cancer is EGFR/ErbB1. Cetuximab is an monoclonal antibody directed against EGFR and erlotinib, gefitinib, lapatinib are tyrosine kinase inhibitors of this pathway.[9,10] Two phase II clinical trial studies on cetuximab derived conflicting data and hence efficacy of cetuximab in liver cancer is yet to be elucidated. Erlotinib is a reversible inhibitor of EGFR thyrosine kinase it improved the survival rate in clinical trial in liver cancer patients. Lapatinib inhibits both EGFR and HER-2. In phase II clinical trial study it showed moderate anti-tumor activity and was well tolerated. Gefitinib is an oral selective inhibitor of EGFR. Clinical trial on gefitinib showed it was not effective as monotherapy in liver cancer. [2,8]

2.4 IGF Inhibitors

Insulin-Like Growth Factor (IGF) pathway consists of circulating ligands, IGF-I and IGF-II, interacting with a membrane receptor, IGF-1R. Aberrant IGF signaling activation has been implicated in the pathogenesis of liver cancer. Pharmacological agents such as OSI- 906, IMC-A12 and AVE-1642 targeting IGF signaling are currently under evaluation in clinical trials on liver cancer patients. [6,10] IMC-A12 [cituxamumab] is a monoclonal antibody and clinical trial conducted along with sorafenib showed long lasting disease stabilization in liver cancer patients.

2.5 mTOR inhibitors and PI3K inhibitors

The PI3K/Akt/mTOR pathway has been implicated in carcinogenesis. When PI3K is triggered, a cascade of downstream effectors such as Akt and mTOR are produced. Preclinical studies have demonstrated that PI3K inhibitors such as perifosine, LY29004 and wortmannin have anti-cancer activity in liver. mTOR inhibitors such as everolimus, temsirolimus, sirolimus are currently used clinically for treatment of other types of cancer. [2,8] Preclinical studies on everolimus, temsirolimus showed anticancer activity and presently clinical trials on the drugs either alone or comination with sorafenib is ongoing

2.6 Wnt inhibitors

Wnt-β-catenin pathway controls biochemical processes related to cell growth and differentiation. Alteration of this pathway leads to liver cancer. Molecular targets of this pathway include Wnt ligands, Frizzled receptors and the β -catenin. Pharmacologic agents targeting Wnt-β-catenin such as PKF118-310, PKF115-584, CGP049090 have showed promising results in pre-clinical studies. [2,9]

2.7 Hedgehog Pathway inhibitors

The hedgehog pathway is essential for embryonic development and cell differentiation. Studies have shown activation of the Hedgehog pathway in liver carcinogenesis suggesting a potential therapeutic target. Hedgehog pathway inhibitors are currently in pre-clinical testing. [6,8]

2.8 c-MET inhibitor:

Mesenchymal epithelial transition factor (c-MET) is activated by binding of hepatocyte growth factor (HGF) and its over- expression is related with liver cancer. Tivantinib is a selective c-MET inhibitor. In phase II clinical trial it improved the survival rate in hepatocellular carcinoma patients. Cabozantinib, foretinib, tepotinib, capmatinib, golvantinib and emibuzumab are other c-MET inhibitors which are currently under study. [2,6]

2.9 Other Pathways and Therapeutic Targets

Fibroblast growth factor (FGF) is an important growth factor implicated in liver cancer. Lenalidomide inhibits FGF and vascular endothelial growth factor (VEGF). Clinical trials on lenalinomide showed 50% decrease in tumor size when treated in advance liver cancer patients. Telomerase, TGF- β are other targets that are being currently under investigation. [11,12]

Clinical trials on molecular targeted drugs as first line or second line or combination therapy for liver cancer have been conducted with variable result. Though combination of molecular targeted therapies is expected to improve the outcome benefits by blocking complementary pathways in cancer, issues such as drug resistance, different responses to targeted drug, drug toxicity are the practical limitations. [12] Hence no favorable conclusions could be derived for most of these pharmacological agents for treatment of liver cancer. So far sorafenib is still the standard treatment for advanced liver cancer.

3. Immunotherapy

The aim of immunotherapy in cancer patients is to facilitate immune response. These include vaccination, antibody-based treatments, adoptive cell therapy, immune checkpoint blockade, and cytokine targeting.

3.1 Vaccine therapy

Tumor associated antigen (TAA) are targeted to overcome immune tolerance by expressing antigenic proteins/peptides or co-stimulatory molecules on tumor cells. Alfa fetoprotein (AFP) was the first targeted TAA as vaccine therapy in liver cancer. Another TAA investigated in liver cancer study is glypican-3 (GPC3), which is over expressed in more than 80% of HCC. *In-situ* cancer vaccine acts by stimulating antitumor immune reaction. Mucin protein 1 (MUC1) was targeted and increased the median survival time and had no adverse effect in clinical trial on liver cancer patient. [13,14]

3.2 Adoptive cell immunotherapy

It involves administration of genetically modified T cell to express an artificial receptor known as chimeric antigen receptors (CARs) or cloned T cell receptors (TCR) to patients after in-vitro expansion. It helps T cells to recognize specific antigens on tumor cells and kill them. The main disadvantage is that CAR-T cells may release massive amounts of cytokines into the patient's blood stream leading to severe adverse effect. [15] Cytokine-induced killer (CIK) cells are in vitro activated autologous and allogeneic T cells, which acquire anti-tumor activity. Studies show that CIK cell treatment declined recurrence and tumor volume in liver cancer patients after non surgical invasive therapy. [16]

3.3 Immune checkpoint inhibitors

T-cell activation is regulated through co-stimulatory and co-inhibitory molecules. Targeting such molecules or their ligands such as Programmed Death-1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), CD160, Lymphocyte Activation Gene-3 (LAG-3), T-Cell Immunoglobulin and Mucin-Domain Containing-3 (Tim-3) has shown to enhance specific immune activation.

PD-1 is a negative co-stimulatory molecule expressed on T cells, B cells, NK cells and myeloid cells. PD-L1 and PD-L2 are ligands for PD-1. They inhibit T cell receptor-mediated lymphocyte proliferation and cytokine production by CD4+ T cells. Administration of anti-PD-1 antibodies releases this inhibition mechanism and allows T cells to remain active. Another immune checkpoint molecule namely, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), regulates the proliferation of activated lymphocytes. Therapy with an anti-CTLA-4 antibody aims to release this opposition on T cell activation in the lymph nodes. Approved immune checkpoint inhibitors include nivolumab and pembrolizumab (anti-PD-1 antibodies) and ipilimumab (anti-CTLA-4 antibody). Clinical trials of monotherapy or combination therapy using one or multiple antibodies against PD-1, PD-L1, and CTLA-4 for the treatment of liver cancer are currently ongoing.

Targeting other immune checkpoint molecules such as CD160, LAG-3, T-Cell Immunoglobulin and Mucin-Domain Containing-3 Tim-3 are under investigation. The main adverse events of using immune checkpoint inhibitiors are hyperthyroidism, hypothyroidism, type 1 diabetes mellitus and myasthenia gravis, rheumatoid arthritis and Addison's disease. [12,17]

3.4 Cytokine therapy

The effects of immune-stimulatory cytokines such as interferon-alpha (IFN-α), interferon-gamma (IFN-γ), and interleukin (IL)-2 have been investigated in clinical trials. However cytokines may induce toxic reactions or produce no significant effects. These elicit a nonspecific immune response or toxic reactions in combination with chemotherapy in liver cancer. [4,5]

4. Gene and stem cell therapy

Gene therapy involves transfer of genetic information to a patient in order to overcome a genetic defect or to provide a protective function. Various gene transfer techniques such as gene directed enzyme/pro-drug therapy, inhibition of oncogenes and restoration of tumor-suppressor genes, immunotherapy, anti-angiogenesis and virotherapy has been studied with little success. [18]

5. Conclusion

Surgery, chemotherapy, radiotherapy and liver transplantation are the main treatments for liver cancer. However due to resistance to conventional therapy, alternative therapeutic strategies are gaining momentum in liver cancer research.

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