Immune-based Therapy Clinical Trials in Hepatocellular Carcinoma

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**Abstract**

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality and continues to increase. Current standard of care for patients with HCC only provides limited therapeutic benefit. Development of innovative strategies is urgently needed. Experience with immunotherapy in HCC is quite early, but rapidly rise in the recent 15 years. Multifaceted immune-based approaches have shown efficacy in achieving disease regression, representing the most promising new treatment approach. Here, we classify the ongoing or completed clinical trials in HCC in terms of the immune strategies to be used and assess their clinical outcomes. The generated information may be helpful in the design of future immune-based therapies for achieving ideal tumor control and maximizing anti-tumor immunity.

**Keywords:** Hepatocellular carcinoma (HCC); Clinical trial; Immunotherapy; Adoptive immunotherapy; Vaccination; Immune checkpoint; Chemoimmunotherapy

**Introduction**

Worldwide, HCC is the second leading cause of cancer-related mortality and continue to increase. Last 20 years, HCC has increased 62% to over 750,000 new cases annually [1,2]. In the united states, HCC is the fastest growing cause of cancer-related death and over 35,000 new cases are annually identified now [3]. Current treatments for HCC only provide limited benefit as survival is poor even for patients with local disease. HCC is refractory to classic chemotherapy and unsuitable for radiation treatment due to liver toxicity [4]. Surgical resection or ablation offers a small chance for cure. Liver transplantation is an effective treatment for cirrhosis and early tumors, but most patients are ineligible because recurrence is common and organs are scarce [5]. The receptor tyrosine kinase inhibitor (RTKI), sorafenib, was the first and only drug approved by the Food and Drug Administration (FDA) to treat unresectable HCC in 2008; however sorafenib only increases the median overall survival of patients from 7.9 to 10.7 months [6]. This small but statistically-significant therapeutic effect highlights the challenge in treating this devastating disease.

It is clear that even after cancer develops, the power of the immune system can be harnessed to suppress tumor growth [7-9]. Although experience with immunotherapy is quite early, multifaceted approaches have shown efficacy in achieving disease regression and even cure [10]. Manipulation of the immune system toward the rejection of established cancers as part of the standard of care is becoming closer to reality [11-13]. Studies of immune checkpoints in tumor-induced immune tolerance greatly advance immunotherapeutic drug development [14,15]. The monoclonal antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) were respectively approved by FDA in 2011 and 2014 for the treatment of patients with advanced melanoma [16]. In March of this year, anti-PD-1 antibodies as the first immunotherapeutic agent for the treatment of squamous non-small cell lung cancer were approved by the US FDA [17]. These exciting progresses support the translation of immunotherapies to other cancers including HCC [18]. Searching for the term “cancer immunotherapy” at https://clinicaltrial.gov/ yields 1167 clinical studies, 124 of which are in phase III clinical trials, 669 of which are in phase II clinical trials and 575 of which are in phase I clinical trials. Among them, 27 clinical trials are used to treat patients with HCC. Here, we classify these ongoing or completed immunotherapy clinical trials and evaluate their therapeutic efficacy. The generated information may be helpful to maximize anti-tumor immunity and design future immune-based therapies for achieving ideal tumor control.

**Rapid rise of immunotherapy clinical trials in HCCs in recent 15 years**

While the function of immunity against cancers was recognized several decades ago, cancer immunotherapy from bench to bedside takes a long time, but rise rapidly in the recent 15 years. In late 1980s, French researchers discovered new protein receptors on the surface of T cells known as CTLA-4 [19]. James Allison, working now at the University of Texas MD Anderson Cancer Center in Houston, found that CTLA-4 functions as a brake to prevent T cells from generating
powerful immune attacks. Initial functional studies suggested that antibodies-mediated blockade of CTLA-4 synergizes anti-CD28 antibodies to enhance T cell activation [20]. In 1996, Alison published a paper in Science showing that antibodies-mediated blockade of CTLA-4 destroyed tumors in mice [21]. In 2010, Bristol-Myers Squibb reported that anti-CTLA-4 antibodies treatment increased average lifespan of patients with metastatic melanoma from 6 months to 10 months [22]. Given this breakthrough success, the anti-CTLA-4 mAb was approved by FDA in 2011 for the treatment of patients with advanced melanoma [16]. Currently, basic and clinical scientists worldwide are working relentlessly to extend the promise to other cancers including HCC. Immune-based therapy clinical trials rise rapidly in recent 15 years. From 1991 to present, total 1167 immunotherapy clinical trials have been found in http://clinicaltrials.gov with about 90% of them conducted in recent 15 years (Figure 1). 27 of them are applied for the treatment of HCC with 25 conducted in the past 15 years (Figure 2). As an outstanding achievement, Science magazine named cancer immunotherapy as the biggest breakthrough of the year in 2013.

Categories of immunotherapy in terms of strategies to be used

Opposed to traditional cancer treatments targeting tumors, cancer immunotherapy targets cancer patients' immune system to fight off cancer cells. Based on strategies used in human HCC clinical trials, immunotherapies fall into four major categories: 1) adoptive immunotherapy, 2) therapeutic vaccination, 3) blockade of immune checkpoint, 4) combinational chemoimmunotherapy. To date, 27 immunotherapies have been conducted in human HCC including 13 in open studies with or without recruiting patients (Table 1) and 14 in closed studies with different status seen in Table 2.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Not yet recruiting</th>
<th>Recruiting</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adoptive therapy</td>
<td>6</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Therapeutic vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blockade of checkpoint</td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Combinational chemoimmunotherapy</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>9</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 1: Open studies of immunotherapy clinical trials in HCC.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Completed</th>
<th>Terminated</th>
<th>Withdrawn</th>
<th>Suspend</th>
<th>Active Not recruiting</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adoptive therapy</td>
<td>4</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Therapeutic vaccine</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Blockade of checkpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combinational chemoimmunotherapy</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 2: Closed studies of immunotherapy clinical trials in HCC.
Adoptive immunotherapy

Adoptive immunotherapy is a form of passive immunization in which autologous effector cells are *ex vivo* sensitized and then given back to the cancer patients. The sensitized effector cells possess cytotoxic function to destroy cancer cells after adoptively transferring into cancer patients. The pioneer trial was conducted by Dr. Steven Rosenberg over 30 years ago with *ex vivo* activated cancer-fighting white blood cells [23]. As one of main immunotherapeutic strategies, adoptive immunotherapy is widely used in the current cancer clinical trials. About half of immunotherapy clinical trials in HCC (12 trials) are adoptive immunotherapy. In these trials, four types of immune cells are used in the adoptive immunotherapy, such as mixed killer cells (13), nature killer (NK) cells (2), nature killer T (NKT) cells (1) (Table 3), and chimeric antigen receptor (CAR) T cells.

Cytokine-induced Killer (CIK) Cells

CIK cells are generated by *ex vivo* incubation of human peripheral blood mononuclear cells (PBMCs) or cord blood mononuclear cells with interferon-gamma (IFN-γ), anti-CD3 antibody, recombinant human interleukin 1 (IL-1) and recombinant human IL-2 [24-26]. The *ex-vivo* expanded CIK cells express CD3 and CD56, featuring a mixed T cell-like and NK cell-like phenotype [27]. The studies demonstrated CIK cells have potent, non-MHC restricted cytotoxicity against tumor cells [24,25,28,29]. The high proliferation rate [25,26], low risk of graft-vs-host disease [30] and easy availability contribute to their advantageous profile, making CIK cells a preferential adoptive immunotherapeutic approach for cancer patients [25,31-33].

Table 3: Clinical trials applying adoptive therapy for treatment of HCC.

In 2000, the impact of a CIK therapy on the postsurgical recurrence rates was conducted in 72 HCC patients who had all undergone hepatic resection (NCT00699816) [34]. The median time for follow-up was 4.4 years. The recurrence rate in CIK cell treatment group was...
significantly lower (59%, 45 patients) than patients in the control group (77%, 57 patients). Also, the time to first recurrence was significantly longer in the CIK treatment group.

In 2004, the phenotypes of CIK effector cells, peripheral T lymphocyte subsets and dendritic cell (DC) subsets were investigated in 13 HCC patients who had liver cirrhosis and more than twenty years of chronic HBV infection [35]. 108 days after CIK cell infusion, the composition of lymphocyte subpopulations was still similar to the levels determined ten days after therapy. This indicates the long-term durable characteristics of CIK cells. Also, in another trial, CIK therapy reduced HBV burden from 1.85 × 10^6 to 1.41 × 10^5 copies of DNA/mL three months after therapy [36]. These results suggest that CIK cells are able to restrict viral infection in addition to tumor control.

In 2008, the impact of CIK therapy on tumor recurrence was conducted in 85 HCC patients who had received transcatheter arterial chemoembolization (TACE) and radio frequency ablation (RFA) [37]. After CIK cell infusions, the frequency of CD4^+ CD3^- CD56^-, CD3^-CD56^+ T cell and the CD4^-CD8^- ratio were significantly increased (P<0.05); whereas the percentage of CD8^- cells decreased from 31.1 ± 7.8% to 28.6 ± 8.3% (P<0.05). The 1-year and 18-month recurrence rates of the study group were 8.9% and 15.6%, compared with 30.0% and 40.0% of the control group (both P value <0.05). Similar results were observed in a study performed by another group in 2010 [38]. The data suggest that CIK cell transfusion capably reduces the recurrence rate of HCC.

In 2009, a randomized study was conducted to investigate the outcome of postoperative CIK cells therapy in 127 HCC patients who underwent radical hepatic resection [39]. The results of a long follow-up demonstrated that adoptive CIK cell therapy can prevent or at least delay recurrence of HCC after hepatic resection. However, adjuvant CIK cell therapy does not seem to be able to improve the overall survival (OS).

In 2013, a retrospective study was conducted in 174 HCC patients from January 1999 to April 2012. Among them, 85 patients were given CIK cell infusion after treatment with TACE and RFA alone [40]. The results demonstrated that CIK cell infusion significantly prolonged the median survival time (MST) and the median progression-free survival (PFS) in patients compared to TACE or RFA monotherapy (MST: 56 months versus 31 months, P=0.023; PFS: 17 months versus 10 months, P<0.001). The 3-, 5-, and 10-year OS was also significantly higher in the CIK group (P ≤ 0.005). This result was supported by another nonrandomized controlled clinical trial conducted in 146 patients [41]. In addition, two groups reported that infusion of ex vivo activated tumor infiltrating lymphocytes (TILs) also decreased the cancer recurrence and prolonged the tumor-free time compared to the control group without receiving TILs [34,42].

In summary, CIK cell infusion in combination with other standard of care is an effective therapy which significantly delays recurrence and increases survival of patients with HCC.

**NK cells**

NK cell is a type of cytotoxic lymphocyte critical to the innate immune system. Phenotypically, NK cells are defined as CD56^+ CD3^- in humans. Receptor diversity allows NK cells exert the different function in response to the challenge with different pathogens including virus-infected cells and neoplastic cells [43,44]. The number of NK cell in the peripheral and tumor is positively correlated with the survival and prognosis of HCC patients [45]. However, NK cells were functionally impaired in advanced HCC patients [46,47]. Impaired NK cells were found to be associated with increase of regulatory T cells (Tregs) [48] and myeloid-derived suppressor cells (MDSCs) [49], resulting in reduction of anti-tumor immune response. Treatment of NK cells with IL-2, IL-12 and IFN-α/β is able to activate their cytotoxic capacity [43,44]. Activated NK cells release cytokines and chemokines to improve both innate and adaptive immune response [50].

A group in the University of Miami has characterized NK cells extracted from living donor liver graft [51]. They observed that the activated NK cells with IL-2 and IFN-γ generate strong cytotoxicity [51]. A phase I safety study of living NK cell therapy for hepatoma liver transplantation (NCT01147380) was started in July, 2010 and completed in December, 2014. An ongoing phase II clinical trial (NCT02008929) was initiated in August, 2014. This trial evaluates the safety and efficacy of MG4101 (ex vivo expanded allogeneic NK cells) as a secondary treatment after curative liver resection on advanced HCC patients with a high risk of recurrence. Both studies have not published the results.

**Chimeric antigen receptor (CAR) T cells**

CAR T cells are the genetic engineering of T cells through the introduction of a chimeric antigen receptor (CAR) [64]. The genetically modified T cells target tumors through the expression of a CAR. CAR design and elements required for the successful eradication of malignancies have been widely studied and tested in various cancers. The results suggest that CAR T cell therapy is a highly promising treatment for cancer and generates the favorable preclinical...
and clinical results [65]. In 2010, FDA approved a phase I/II study of CAR T cells in subjects with different cancers by targeting VEGFR2 (NCT01218867). HCC patients without hepatitis B and C are included; however, no result has been posted.

**Cancer vaccine**

Cancer vaccines help the immune system to recognize and attack cancer cells. There are two types of cancer vaccine. Treatment of existing cancer is known as therapeutic cancer vaccines. Prevention of cancer from developing in healthy people is known as preventive vaccine. While prophylactic HBV and HCV vaccines contribute to the decrease of HCC patients [66], therapeutic vaccines for HCC are still awaited due to presence of other risk factors and the increased prevalence of non-alcoholic fatty liver disease [67,68]. To date, eight vaccine clinical trials in HCC patients were completed or are ongoing with 4 trials in phase I, 2 in phase I/II and 1 in phase III (Table 4). The vaccines targeting HBV and HCV are beyond the scope of current review and not introduced here.

Table 4: Clinical trials of tumor vaccine on hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Registered No.</th>
<th>Intervention</th>
<th>Vaccine Type</th>
<th>Start Year</th>
<th>Patient</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00610389</td>
<td>DC loaded with autologous tumor</td>
<td>Therapeutic vaccine</td>
<td>2008</td>
<td>Metastatic HCC</td>
<td>II</td>
<td>Clinica Universidad de Navarra</td>
<td>Unknown</td>
</tr>
<tr>
<td>NCT01128803</td>
<td>Autologous DCs loaded with AFP peptides</td>
<td>Therapeutic vaccine</td>
<td>2009</td>
<td>AFP ≥ 40 ng/ml</td>
<td>I/II</td>
<td>Nantes University Hospital</td>
<td>Terminated</td>
</tr>
<tr>
<td>NCT00669136</td>
<td>AFP + GM-CSF plasmid prime and AFP adenoviral vector boost</td>
<td>Therapeutic vaccine</td>
<td>2009</td>
<td>Locoregionally treated HCC</td>
<td>I/II</td>
<td>Lisa H. Butterfield, Ph.D.</td>
<td>Terminated due to poor accrual</td>
</tr>
<tr>
<td>NCT01828762</td>
<td>Autologous DCs incubated with irradiated autologous tumor stem cells and suspended in GM-CSF</td>
<td>Therapeutic vaccine</td>
<td>2012</td>
<td>Candidates for resection</td>
<td>I</td>
<td>Cellular Biomedicine Group Ltd.</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT01522820</td>
<td>DEC-205NY-ESO-1 fusion protein CDX-1401 vaccine</td>
<td>Therapeutic vaccine</td>
<td>2012</td>
<td>After resection and TACE</td>
<td>I</td>
<td>Roswell Park Cancer Institute</td>
<td>Not recruiting</td>
</tr>
<tr>
<td>NCT01974661</td>
<td>Allogenic DC based therapeutic vaccine</td>
<td>Therapeutic vaccine</td>
<td>2013</td>
<td>Not eligible for curative treatment or TACE</td>
<td>I</td>
<td>Immunocore AB</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01923233</td>
<td>ALLOSTIM(TM) in-situ vaccine in combination with RFA</td>
<td>Therapeutic vaccine</td>
<td>2013</td>
<td>Refractory HCC</td>
<td>I</td>
<td>Immunovative Therapies, Ltd.</td>
<td>withdrawn prior to enrollment</td>
</tr>
<tr>
<td>NCT02232490</td>
<td>hepcortespenilumit-L (V5)</td>
<td>Therapeutic vaccine</td>
<td>2015</td>
<td>Advanced HCC</td>
<td>III</td>
<td>Lisichanak Regional Tuberculosis Dispensary</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

| **A**AFP: α-fetoprotein; DC: Dendritic Cell; GM-CSF: Granulocytes Macrophage Colony-Stimulating Factor; HCC: Hepatocellular Carcinoma; TACE: Transarterial Chemoembolization; RFA: Radiofrequency Ablation |

Butterfield et al. used CD8+ T-cell epitopes specific for alpha fetoprotein (AFP) to carry on the first HCC vaccine clinical trial. The results showed the generation of AFP-specific T-cell responses in vaccinated subjects [69]. Subsequently, Butterfield et al. conducted another phase I/II trial with autologous DCs ex vivo pulsed by AFP epitopes. These DCs are large, granular lymphocytes with high expression of MHC class I, MHC class II, and CD86 and expected to enhance immune response [70]; however, this trial only resulted in transient CD8+ T-cell responses, possibly caused by the lack of CD4+ help [71]. The similar clinical trial was conducted in 2010 by another group from France (NCT01128803), but was terminated without result reported. In addition, autologous DCs pulsed ex vivo with the lysate of the autologous tumor [72], HepG2 cells [73] and telomerase peptides [74], have been evaluated in human clinical trials. Unfortunately, all of the studies only showed limited improvements in clinical outcomes. A new phase I trial on DC vaccine was registered last year and is now recruiting participants (NCT01974661). Some strategies including DC immunotherapy combined with local radiation [75] or TACE [76] were also used in HCC clinical trials, but no significant impact on prevention of tumor recurrence was detected. In January, 2015, a phase III clinical trial was started to seek the therapeutic benefit of hepcortespenilumit (V5) in subjects with advanced HCC (NCT02232490). Efficacy of this trial will be evaluated by measuring AFP level over the treatment and monitoring tumor change in initial time and end time by CT-scan.

In summary, current vaccine monotherapy doesn’t generate significant clinical outcome in patients with HCC.

**Blockade of checkpoint**

Immune checkpoints are critical modulators in the immune system that either turn up a signal (co-stimulatory molecules) or turn down a signal (co-inhibitory molecules). The balance between costimulatory signals and inhibitory immune checkpoints determines the cytotoxic T-cell activation and intensity of immune response [77,78]. It is now clear that tumors modulate immune checkpoints as one of the mechanisms to escape immune surveillance and rejection [79]. Since around 2010 checkpoint molecules have been increasingly considered as new targets for cancer immunotherapies due to the effectiveness of two checkpoint inhibitor drugs in the treatment of advanced cancer.
melanoma [80]. Owing to the great achievement, immune checkpoint blockade therapy sheds light on other solid tumors including HCC. Antibodies-mediated blockades of CTLA-4 and PD-1 are currently being tested in HCC clinical trials. Five anti-PD-1 antibodies and three anti-PD-L1 antibodies are currently under development (Table 5), emphasizing the growing interest in these immune checkpoint pathways as a target for cancer therapy [77].

Table 5: Clinical trials of checkpoints blockade on hepatocellular carcinoma.

<table>
<thead>
<tr>
<th>Registered No.</th>
<th>Intervention</th>
<th>Patient</th>
<th>Phase</th>
<th>Start Year</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01008358</td>
<td>CP 675.206 (tremelimumab) - Anti-CTLA antibody</td>
<td>Unresectable HCC</td>
<td>II</td>
<td>2008</td>
<td>Clinica Universidad de Navarra, Universidad de Navarra</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT00966251</td>
<td>Pidilizumab – anti-PD1 antibody</td>
<td>Not operational HCC</td>
<td>I/II</td>
<td>2009</td>
<td>CureTech Ltd.</td>
<td>Terminated due to slow accrual</td>
</tr>
<tr>
<td>NCT01658878</td>
<td>Nivolumab – anti-PD1 antibody</td>
<td>Advanced HCC</td>
<td>I</td>
<td>2012</td>
<td>Bristol-Myers Squibb</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01853618</td>
<td>Tremelimumab – anti-CTLA4 antibody</td>
<td>Advanced HCC</td>
<td>I</td>
<td>2013</td>
<td>National Cancer Institute (NCI)</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02519348</td>
<td>MEDI4736 (anti-PD-L1 antibody), tremelimumab (anti-CTLA4 antibody)</td>
<td>unresectable HCC</td>
<td>I/II</td>
<td>2015</td>
<td>MedImmune LLC</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>

Table 6: Clinical trials of combination therapy on hepatocellular carcinoma.
In 1999, a phase II study of doxorubicin and IL-2 in unresectable HCC was initiated and completed in 2001 without results reported. This trial is to evaluate the immunological response and tumor response in patients with unresectable HCC to doxorubicin and protracted recombinant IL-2. In addition, PFS and OS of this patient population after treatment with this regimen is assessed. Another two chemoinmunotherapies were initiated in 2012 and 2015, but not recruiting participants.

Prerequisite for successful chemoinmunotherapy requires chemotherapy induces favorable environment allowing immunotherapy to exert effective cancer cytotoxic function. Ideal chemotherapy drug is capable to generate immunogenic cell death and block tumor-induced immune tolerance [85] which involve in the release of tumor antigens, emission of danger-associated molecular patterns (DAMP), the activated expression of the pattern recognition receptor (PRR) Toll-like receptor 3, rapid secretion of type I IFNs, and the release of the chemokine CXCL10, etc. In addition, the effect of chemotherapy on antitumor immunity is a drug-, dose-, and schedule-dependent manner [86]. Thus, to design effective chemoinmunotherapy regimens, clinical investigators should consider how chemotherapy impacts the immune system and perform the early-phase clinical studies for defining the optimal drug dose and timing in relation to immunotherapy [86].

Future Perspectives

Notably, the powers of immune system can be exploited to destroy tumors. Given immune system’s amazing power with capacity for memory, exquisite specificity plus central and universal role in human biology, immunotherapy has the potential to achieve complete, long-lasting remissions and cancer cures, representing the most promising new cancer treatment approach with few or no side effects.

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