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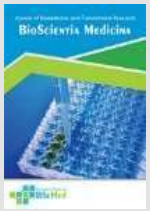

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The Role of Anti-PD 1 (Programmed Cell Death-1) (Pembrolizumab) in Hepatocellular Carcinoma: A Narrative Literature Review

Nelila Pasmah Fitriani[1*], Suyata[2]

[1]Subspecialized Residency Training, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[2]Subdivision of Gastroenterohepatology, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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***Corresponding author:**
Nelila Pasmah Fitriani

E-mail address:
dr.fitri1919@gmail.com

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A B S T R A C T

Hepatocellular carcinoma (HCC) is a malignant tumor originating from liver cells, HCC occurs in around 85% of patients diagnosed with cirrhosis. Treatment options for HCC consider liver function, extrahepatic spread, invasiveness, and the number and size of nodules. HCC therapy options include surgical resection, liver transplantation, tumor ablation, transarterial therapy and systemic chemotherapy. Pembrolizumab is a second-line systemic therapy option for the treatment of HCC after sorafenib therapy. Pembrolizumab is a class of immune checkpoint inhibitors (ICIs) and more specifically works as a programmed cell death-1 (PD-1) inhibitor.

1. Introduction

Hepatocellular carcinoma (HCC) is a malignant tumor originating from liver cells. It is the most common type of primary liver tumor, accounting for more than 90% of cases. HCC occurs in approximately 85% of patients diagnosed with cirrhosis and is the fourth leading cause of cancer death worldwide. HCC is estimated to be the fifth most commonly diagnosed cancer in men (554,000 new cases per year) and ninth in women (228,000 new cases per year). HCC has a mortality ratio of 0.91, occurs 2.3 times more frequently in men than women, and accounts for 72% of new cases diagnosed in Asia each year. The main risk factors for HCC include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin-contaminated foodstuffs, heavy alcohol consumption, and type 2 diabetes. According to the latest statistics, approximately 50–80% of HCC cases worldwide are caused by HBV infection. When diagnosed, HCC is usually multinodular due to early spread in liver cells, then has a high affinity to grow in blood vessels, which continues to invade the portal vein or hepatic vein. Recommendations for HCC treatment differ from one region to another, indicating that there is still a lack of strong scientific evidence to explain the mechanisms of the disease.[1]

When the tumor has not progressed beyond the liver, the treatment options that can be given are locoregional therapy, such as liver transplantation, percutaneous ablation resection, transarterial

chemoembolization (TACE), and radioembolization. The therapy is highly dependent on tumor burden, location, and comorbidities. However, due to the strong and widespread resistance of HCC to cytotoxic chemotherapy, systemic therapy was a deferred option in the management of HCC for many years. Various studies have reported advances in systemic therapy in the last 5 years. Multikinase inhibitors (MKIs) have become standard therapy for advanced HCC, especially soranefib, which targets the vascular endothelial growth factor receptor. vascular endothelial growth factor receptor (VEGFR) 1, VEGFR2, VEGFR3, Raf proteins (BRAF, c-CRAF), platelet-derived growth factor receptor-beta, and other cell surface kinases such as KIT, FLT-3, RET/PTC. When compared with placebo, Sorafenib demonstrated superior efficacy with prolongation of overall survival (OS) from 7.9 to 10.7 months. The first-line MKI alternative is lenvatinib targeting VEGFR1–3 with a median OS of 13.6 months. Recommended second-line therapies are regorafenib and cabozantinib and the monoclonal antibody (mAb) drug ramucirumab targeting VEGFR2; the latter is most effective in patients with alpha-fetoprotein (AFP) >400 ng/mL.[2]

Furthermore, a new era in cancer treatment was marked by the discovery of immune checkpoint inhibitors (ICIs). ICI is an IgG receptor mAb that blocks the cytotoxic molecules T-lymphocyte–associated antigen 4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death-1 ligand-1 (PD-L1). During the immune response, PD-1 functions to reduce T-cell activity to prevent autoimmune damage from occurring. In the case of chronic infections, prolonged antigen exposure results in permanent PD-1 expression that may limit immune-mediated pathogen clearance. Then, PD-L1 expression in HCC cells inhibits T cell function in the tumor microenvironment, so high PD-L1 expression in tumor cells becomes a predictor of recurrence in HCC patients. PD-1 and PD-L1 blockade has been shown to produce impressive and long-lasting anti-tumor effects in a variety of tumor types. Agents targeting PD-1/PD-L1 have started a revolution in HCC treatment.[4] In September 2017, the Food and Drug Administration (FDA) approved the use of the anti-PD-1 antibody nivolumab as a second-line treatment in high-stage HCC patients before sorefenib. It was reported that the objective therapeutic response rate was 20% in patients treated with stable doses of nivolumab and 15% in the dose escalation phase, without differences in the etiology of the underlying liver disease. Similarly, the effectiveness of the anti-PD-1 inhibitor pembrolizumab was investigated in a phase 2 study for second-line treatment in advanced HCC patients after sorafenib failure. This study confirmed an objective response rate of 17%. Thus, the FDA approved pembrolizumab for the treatment of HCC patients who had previously been treated with sorafenib in November 2018. Although there was an improvement in patient clinical outcomes, it had several disadvantages, such as anti-PD-1/PD-L1 results, which were still inefficient in 80% of HCC patients. It is expensive and causes many severe side effects.[3,4]

Mechanism and regulation of anti-PD-1 in hepatocellular carcinoma

The PD-1 (programmed cell death protein) molecule is an accessory receptor for immunosuppressive signals that is expressed on activated T cells, B cells, and myeloid cells. PD-1 works as an antigen-specific inhibitor of T cell activity by binding to PD-L1 and PD-L2. Once bound to each other, these ligands induce two mechanisms in the lymph nodes and in the local environment of the tumor. The first in antigen-specific T-cells in the lymph nodes will induce apoptosis (programmed cell death) while reducing apoptosis in regulatory T-cells (Tregs) and reducing their functionality by blocking T-cell receptor (TCR) and CD28 signaling. The second is in the local tumor environment: binding of PD-L1 to PD-1 on T-cells creates T-cell dysfunction, T-cell exhaustion, and neutralization. PD-1 is expressed mainly on T-cells in late stages of activation, for example, after infection or inflammatory response. Once the T cell receptors on activated T cells recognize

tumor antigens presented by MHC class 1 tumor cells, the T cells release perforin and granzymes to attack the tumor. At the same time, T cells release cytokines such as IFN-γ from $CD8^+$ T cells to bind to the IFN-γR receptor, which triggers the expression of the PD-L1 molecule by nearby tumor cells as a mechanism of protection; meanwhile, T-cell receptor signaling regulates the expression of PD1 on the surface of T cells. The PD-L1 molecule binds to PD-1, triggering a signal that negatively impacts cytotoxic T cell-mediated tumor immune activity, reducing T cell activity and resulting in tolerance immune cells. Administration of PD-1 antibodies (anti-PD-1) such as pembrolizumab can unlock immune "brake" mechanisms, restoring the immune system's ability to attack tumor cells by focusing on tumor cells to restore a strong and accurate host immune system.[5,6]

Signaling pathways in hepatocellular carcinoma

In HCC, changes in liver tissue induced by either chronic viral infection or exposure to hepatotoxic agents lead to the upregulation of a number of components of cellular signaling pathways. Tumor initiation and progression in HCC are significantly influenced by many growth factors, including epidermal growth factor (EGF) receptor, insulin-like growth factor (IGF) receptor, fibroblast growth factor (FGF) receptor, hepatocyte growth factor (HGF/c-MET), stem cell growth factor receptor, platelet-derived growth factor (PDGF) receptor, and vascular endothelial growth factor (VEGF) receptor.[7,8]

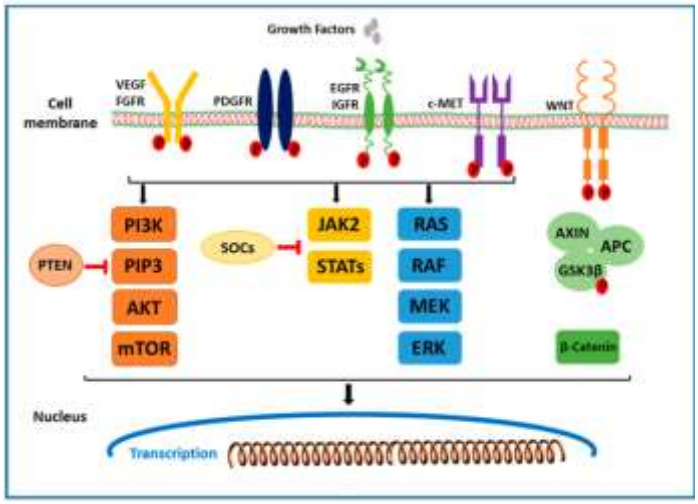

Figure 1. Schematic representation of the HCC signaling pathway.

IGF-2 is overexpressed in human HCC, and excess availability of this ligand leads to increased receptor binding and further actions on the MAPK and PI3K/AKT/mTOR pathways. In the PI3K/AKT/mTOR signaling pathway, a family of enzymes is activated by binding several growth factors (IGF and EGF) and cytokines to receptors. Upon activation, PI3K produces the lipid second messenger phosphoinositol triphosphate (PIP3) and related second messengers, which, in turn, activate AKT/protein kinase B (PKB). Akt is a threonine kinase downstream of PI3K. Activated Akt phosphorylates several cytoplasmic proteins and regulates various cellular activities, including the induction of transcription of genes that drive cell proliferation. The JAK/STAT signaling pathway is activated by many cytokines, hormones, and growth factors. In this pathway, cytokines induce phosphorylation of the JAK family, consisting of the four members Jak1, 2, 3, and Tyk2, followed by activation of the six Stat family members 1, 2, 3, 4, 5, and 6. Tyrosine phosphorylation by JAK results in activation of the pathway This. It is involved in various functions such as differentiation, proliferation, and apoptosis. The Raf/MEK/ERK signaling pathway is a

signal transduction pathway that regulates important intracellular processes, including cell proliferation, differentiation, angiogenesis, and survival. This pathway is activated by the binding of several growth factors to the receptor, triggering a series of phosphorylation events.[9]

The Wnt/-Catenin signaling pathway consists of Wnts, which secrete cysteine-rich glycoprotein ligands. Frizzled family member Wnt ligands on the cell surface, resulting in phosphorylation and inhibition of GSK3, which is associated with increased cytosolic β-catenin concentrations. Wnt ligands, binding to ten transmembrane frizzled receptors, lead to activation of either the canonical (β-catenin-dependent) or non-canonical (β-catenin-independent) Wnt pathways. Cytosolic β-catenin forms a complex with adenomatous polyposis coli (APC) and AXIN1 or AXIN2, mediating sequential phosphorylation and degradation of β-catenin by casein kinase 1 and glycogen synthase kinase 3. This causes the translocation of β-catenin to the nucleus, where it interacts with TCF and LEF transcription factors and activates the transcription of genes involved in cell proliferation. angiogenesis (VEGF, c-MET), anti-apoptosis, and extracellular matrix formation.[10]

Pembrolizumab

Anti-PD1 is the main systemic therapy in clinical practice that has been proven to produce impressive anti-tumor effects in various types of tumors. 4 In HCC, adaptive immune resistance occurs, and tumor cells induce PD-L1 for protection against immune cell-mediated damage due to infection. When PD-L1 binds to PD-1 (which is expressed on activated T cells), T-cell function is inhibited; Pembrolizumab blocks PD-1 and PDL-1 complex formation, allowing for increased T-cell-mediated killing immune activity. Pembrolizumab was first approved for the treatment of metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck squamous cell carcinoma, recurrent locally advanced or metastatic gastric cancer, locally advanced or metastatic urothelial cancer, and classic Hodgkin's lymphoma. The results of the KEYNOTE-224 trial led the FDA to approve pembrolizumab as a second-line agent for the treatment of HCC after sorafenib therapy. Pembrolizumab is approved by the FDA to treat advanced HCC by inhibiting the first immune checkpoint activity in hepatocytes. Pembrolizumab is a humanized monoclonal IgG4 kappa antibody directed against cell surface PD-1 on lymphocytes. The presence of PD-1 receptor inhibition is expected to inhibit immune check-point activity so that there is no inhibition of the response. When PD-1 ligands, PD-L1, and PD-L2, bind to the PD-1 receptor found on T-cells, T-cell proliferation and cytokine production are inhibited, thereby preventing the immune system from attacking cancer cells. Upregulation of this ligand occurs on the cell surface of several tumors, including HCC, effectively reducing active T cell surveillance of the tumor. Pembrolizumab binds to the PD-1 receptor with high selectivity, inhibits the interaction of PD-1 with its ligand, and allows T cells to attack cancer cells.[11]

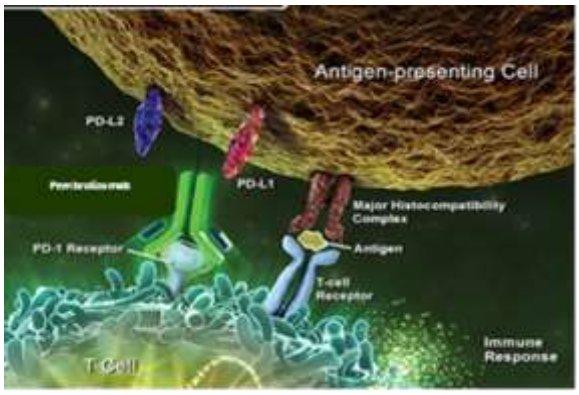

Figure 2. Working mechanism of pembrolizumab.

Pembrolizumab as first-line HCC therapy

The KEYNOTE-224 (NCT02702414) cohort 2 trial was conducted to determine the effect of pembrolizumab in the treatment of advanced HCC that had not received previous therapy. This research is an open-label study and phase II trial in a multi-country. The sample consisted of advanced HCC patients who were not amenable to or refractory to locoregional therapy and had not previously been treated with systemic therapy. Patients were given pembrolizumab 200 mg intravenously every 3 weeks for ≤ 2 years. The results of this trial show that pembrolizumab as monotherapy has promising antitumor efficacy and survival outcomes. In general, as first-line monotherapy, the safety profile of pembrolizumab is acceptable and consistent with that of previous studies. Treatment-related adverse events were reported in 28 (55%) patients, with most severity grades 1 to 2. The median time from the first dose to data cutoff was 27 months (range, 23–29) with objective response rate (ORR) values of 16% [95% CI, 7–29]; results were similar across major subgroups. Median duration of response (DOR) was 16 months (range, 3-24 years), disease control rate (DCR) was 57%, median progression-free survival (PFS) was 4 months (95% CI, 2-8), median time to progression (TTP) was 4 months (95% CI, 3–9), median overall survival (OS) was 17 months (95% CI, 8–23), and treatment-related grade ≥ 3 adverse events occurred in 16% of patients.[12]

Pembrolizumab as second-line HCC therapy

The results of the KEYNOTE-224 trial led the FDA to approve pembrolizumab as a second-line agent for the treatment of HCC after sorafenib therapy. The KEYNOTE-224 study was a non-randomized, open-label, multicenter phase II study in which 104 patients were treated with intravenous pembrolizumab (200 mg) every 3 weeks for 2 years or until disease progression or discontinuation for other reasons. The study treatments included patients who were refractory or intolerant to sorafenib (group 1) and patients who had not received prior systemic therapy (group 2). The objective response rate was 17% (complete 1%; partial 16%). 44 patients (44%) had a stable disease course, while 34 patients (33%) had a progressive disease course. However, serious side effects occurred in 15% of patients. One died of therapy-related ulcerative esophagitis. Subsequently, the phase III KEYNOTE-240 Study was carried out, which confirmed the efficacy of pembrolizumab in advanced HCC. Patients were divided into two groups: PEMBRO with best supportive care (BSC) and placebo with BSC. A total of 413 patients with a history of sorafenib treatment, Child-Pugh class A, not infected with hepatitis B or C viruses, and who were ECOG PS 0–1 were studied in this study. The authors reported that the ORR was 16.9% (n = 47) and 2.2% (n = 3) in the PEMBRO + BSC and placebo + BSC groups, respectively (p = 0.00001); Although the final analysis showed improved overall survival compared with placebo, the difference did not reach statistical significance by prespecified criteria (HR=0.781; 95% CI=0.611-0.998; p=0.0238). Additionally, patients treated with pembrolizumab experienced improved progression-free survival, but this difference also did not reach the predetermined significance threshold. Currently, a Phase III trial with 5 Asian countries is underway (KEYNOTE-394, NCT03062358).[13]

Pembrolizumab as a combination therapy

In previous trials, the phase 1b trial had investigated the combination of lenvatinib and pembrolizumab as first-line therapy in 100 unresectable HCC patients, showing durable objective radiographic responses with tumor response evaluation values, mRECIST (modified response evaluation criteria in solid tumors) of 46%, with a median PFS of 9.5 months and median overall OS of 22 months. However, the phase III trial, The LEAP-002 (NCT03713593), found that adding pembrolizumab to lenvatinib as a first-line combination did not provide a significant improvement in PFS or OS of advanced HCC patients who had not received prior systemic therapy. The results of the trial showed that in the pembrolizumab group, the median OS was 21.2

months (hazard ratio [HR], 0.840; 95% CI, 0.708-0.997; P = 0.0227), the 24-month OS rate was 43.7% (HR, 0.867; 95% CI, 0.734-1.024; P =.0466), Median PFS 8.2 months, ORR 26.1%, DOR 16.6 months, and Grade 3-4 treatment-related adverse events (TRAEs) occurred in 61.5% of patients. Meanwhile, in the placebo group, the Median OS was 19.0 months, and the OS rate was 40.0%. Median PFS was 8.0 months, ORR 17.5%, DOR 10.4, and TRAEs occurred in 56.7% in the placebo group. This does not meet the previously determined threshold of excellence.[14]

Indication

Pembrolizumab initially received FDA approval for the treatment of advanced, refractory melanoma. It further developed and has received approval for the treatment of other oncologic conditions, such as metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head, and neck squamous cell carcinoma, recurrent locally advanced or metastatic gastric cancer, locally advanced or metastatic urothelial cancer and classic Hodgkin's lymphoma. In cases of (HCC), pembrolizumab is indicated as the first-line in HCC patients who have never received previous therapy. Patients were given pembrolizumab 200 mg intravenously every 3 weeks for ≤ 2 years, with an ORR of 16% and a median DOR of 16 months. Treatment with pembrolizumab resulted in an objective response rate of 18%. With a recommended dose of 200 mg every 3 weeks, ≥ 90% target engagement can be achieved.[15]

Contraindications

There are no contraindications for pembrolizumab. Limitations of use: Pembrolizumab is not recommended in PMBCL (primary mediastinal large B-cell lymphoma) patients who require urgent cytoreductive therapy. The safety and effectiveness of pembrolizumab in MSI-H (microsatellite instability-high) pediatric central nervous system cancers have not been established as this population meets the exclusion criteria of the clinical trial.[14]

Efficacy

In the phase II trial KEYNOTE-224 trial (NCT02702414), patients received 200 mg of pembrolizumab intravenously once every 3 weeks for 2 years. The average time from the first dose to the data cutoff was 27 months with an objective response rate (ORR) of 16%, average duration of response (DOR) was 16 months, disease control rate (DCR) was 57%, median progression-free survival (PFS) was 4 months (95% CI, 2-8), median time to progression (TTP) was 4 months (95% CI, 3-9), median overall survival (OS) 17 months, as well as effects Treatment-related grade ≥ 3 adverse events occurred in 16% of patients.[15]

Side effects

Common side effects occurring in more than 10% of clinical trial participants include Nervous system (headache), Musculoskeletal (back pain, arthralgia) Skin (vitiligo, rash, pruritus) Metabolism (decreased appetite, weight loss, hyponatremia) Respiratory (cough, dyspnea) General (fatigue, pyrexia, asthenia, influenza-like illness, peripheral edema Gastrointestinal (diarrhea, constipation, abdominal pain, nausea, vomiting) Endocrine (hypothyroidism, hyperthyroidism), Infection (pneumonia, urinary tract infection, upper respiratory tract infection) Cardiac (arrhythmia) Blood/lymphatic (anemia) Hepatobiliary (hepatoxicity, increased liver function tests) Kidney and urinary (hematuria, increased blood creatinine). As a PD-1 inhibitor, pembrolizumab has unique side effects. PD-1 inhibitors can block negative regulatory signals of T cells to stop immune suppression and enhance the anti-tumor effect of T cells. However, this mechanism can also overactivate T cells, leading to an imbalance in immune tolerance and carrying out autoimmune-like inflammatory responses called immune-related adverse events (irAEs) when it affects normal tissues, including the skin, digestive tract, liver, endocrine glands, lungs, and so on. A meta-analysis has shown that serious organ-specific irAEs are rare, but the rate of these events is increased with pembrolizumab compared with standard treatment. The most common and earliest irAEs are skin

toxicities, including follicular dermatitis, erythematous dermatitis, and popular dermatitis. Gastrointestinal reactions mostly occur 5 to 10 weeks after application of pembrolizumab. Clinical manifestations are mainly diarrhea and colitis. Immunotherapy-associated pneumonia caused by PD-1/PD-L1 inhibitors primarily manifests as non-specific interstitial pneumonia, which usually occurs anytime between 2 weeks and 2 years. After using pembrolizumab, immunotherapy-associated pneumonia develops in 3-8% of patients and, in some patients, can be life-threatening. Among patients treated with pembrolizumab, approximately 10% were observed to have varying degrees of immune-related endocrine disorders, of which thyroid dysfunction and pituitary inflammation were more common, and type I diabetes has also been reported.[16,17]

2. Conclusion

Treatment options for HCC consider liver function, extrahepatic spread, invasiveness, and the number and size of nodules. HCC therapy options include surgical resection, liver transplantation, tumor ablation, transarterial therapy, and systemic chemotherapy. Pembrolizumab is a second-line systemic therapy option for the treatment of HCC after sorafenib therapy. Pembrolizumab is a class of immune checkpoint inhibitors (ICIs) and, more specifically, works as an inhibitor of programmed cell death-1 (PD-1). Pembrolizumab inhibits PD-1 activation in downregulating cytotoxic T-cell responses so that PD-1 does not bind to its ligand and stimulates activation and proliferation of $CD8^+$ T cells, which results in increased T-cell survival, making it useful for restoring normal antitumor immune responses that are suppressed by the PD-1 pathway. The results of the KEYNOTE-224 trial led the FDA to approve pembrolizumab as pembrolizumab indicated as the first line in HCC patients who have never received previous therapy, with an ORR value of 16% and an average DOR of 16 months. The recommended dose of pembrolizumab is 200 mg every 3 weeks. As a PD-1 inhibitor, pembrolizumab has side effects in the form of immune-related inflammatory responses such as skin toxicity, gastrointestinal reactions, pneumonia, and endocrine disorders. In the future, further investigation of the immune biology of HCC is needed to facilitate the development of more effective therapies in patients with HCC.

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