

The effectiveness of Nivolumab as a monotherapy or combinatory medication for the treatment of hepatocellular carcinoma

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Abstract. HCC remains one of the most malignant tumors worldwide. A high percentage of HCC patients have already grown into advanced stages with little possibility of receiving curative resection or ablation upon confirmed diagnosis. The FDA has granted fast-track (accelerated) approvals to Nivolumab for HCC previously treated with Sorafenib and a combination of Nivolumab and Ipilimumab for Hepatocellular carcinoma. However, more discoveries of Nivolumab-regarding strategies with significantly improved prognosis over standard therapy and solid confirmation are still needed. This review summarizes the newly updated mechanisms and the influence of Nivolumab on the tumor microenvironment of all HCC stages. The released clinical trials between 2016 and 2024 are combined and summarized, with the review focused on trials after 2020. Three trends of clinical research are concluded. As a review including newly-released first results in clinical trials in 2024, this article suggests some future directions based on novel promising data, such as first-line therapy invention and further biomarker utilization. However, the drug resistance against Nivolumab remains not fully clarified.

Keywords: Nivolumab, immunotherapy, HCC, monotherapy.

1. Introduction

Hepatocellular carcinoma (HCC) is a primary tumor of the liver. It counts around 90% of all the primary hepatoma cases worldwide which is characteristic of high morbidity and mortality rates. Besides the considerable distribution of total cases around the world, Hepatocellular carcinoma also shows a higher occurrence in Asia region with inducers such as hepatitis more regularly developing. The overall severity and higher morbidity among certain regions highlight the urgent need for discovering effective therapeutic strategies and trials of medication efficacy among specific ethnicities. Immunotherapy has emerged as a promising strategy among current advancements in cancer medication. Nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, has shown potential in treating various cancers, including HCC. Research into the efficacy of Nivolumab, both as a monotherapy and as part of a combination with other anti-cancer treatments, is crucial in improving the prognosis for HCC patients. Traditional clinical strategies such as liver transplantation, surgical resection, and localized chemotherapies have shown restricted applicability and effectiveness, especially in advanced phases.

Targeted therapies for the first-line medication of inoperable HCC cases include Sorafenib, which offers limited efficacy and modest improvement in prognosis, underscoring the need for alternatives with higher specificity and better effectiveness. Immunotherapy, particularly with agents such as Nivolumab, offers a novel mechanism of action by keeping tumor cells from suppressing the immune system, potentially improving patients' outcomes. Furthermore, Nivolumab may possess the potential flexibility to contribute to combinatory anti-HCC drug development. The research on Nivolumab combined with Sorafenib or other traditional anti-tumor medications could deepen the understanding of various tumor-suppressing routes triggered by this combinatory treatment, thus advancing the development of Nivolumab-involved combinatory anti-HCC treatment with synergistic effects.

Up to now, the FDA has granted accelerated approval to Nivolumab for HCC previously treated with Sorafenib or Nivolumab and Ipilimumab combinatory medication for Hepatocellular carcinoma, which shows the accreditation on Nivolumab efficacy demonstrated in previous phase-one and two trials. However, the collection of abundant data from phase-three clinical trials on Nivolumab against HCC patients with or without primary treatment is underway. Apart from relatively limited data acquired from completed clinical trials, previous research before 2024 mainly focused on studies such as CheckMate-040, an open-label, multicohort, phase I/II study of Nivolumab alone or in combination with other agents in patients with advanced HCC. A series of completed trials in 2020-2024 are worthy of being attached with more attention for the conclusion to unearth new working mechanisms, better anti-HCC combinations, novel inter-drug reactions, and promising directions for the development of future Nivolumab-involved anti-HCC treatments. Hence, based on clinical trials done and finished between 2019 and 2024, this review aims to summarize the current discoveries regarding Nivolumab efficacy both as a monotherapy and in combination with other medications in HCC patients of various stages. Newly revealed inter-drug reactions and mechanisms of Nivolumab resistance are also to be summarized to aid in discussing obtained results from trials and other studies.

2. Working mechanisms

Programmed cell death 1 protein (PD-1) is encoded by the PDCD1 gene inside the human body. It is a cell receptor usually found on the activated T and B lymphocytes. PD-1 can specifically bind to unique ligands, PD-L1 and PD-L2. These ligands are generally expressed on immune-related cells, including T and B lymphocytes, and antigen-presenting cells (APCs) such as macrophages and dendritic cells. In HCC patients, PD-L1 is usually expressed in tumor cells, hepatocytes, and Kupffer cells [1]. Normally, the binding of PD-1 and PD-L1 works as a protective mechanism as they inhibit the immune responses of self-reactive T cells, thus preventing self-reactive T lymphocytes from attacking normal cells. This is considered a vital part of immune tolerance, which effectively lowers the risk of pathogenic autoimmunity [2]. However, HCC patients have malignant hepatocytes with aberrant expression of PD-L1. They utilize this tolerance as an escape strategy and deactivate the PD-1-expressing, tumor-infiltrating T cells [3] by dampening their abilities of malignancy recognition. As a result, the elimination of tumor cells will be inhibited through PD-1/PD-L1 binding.

As a human-origin monoclonal antibody, Nivolumab functions as an immune checkpoint inhibitor, which specifically binds to PD-1 and silences its binding with PD-L1. The whole escape procedure of tumor cells is interrupted. In the meantime, the activation of T lymphocytes targeting HCC tumor cells is initiated. Various signaling pathways are involved to facilitate tumor cell elimination.

The pharmacokinetics of Nivolumab are significant aspects as they imply how the patient's body responds to this treatment upon administration. Four major aspects, absorption, distribution, metabolism, and elimination, are worthy of attention. As documented in the guidance of administration, Nivolumab is given intravenously via infusion. This route of administration is characteristic of a relatively high bioavailability. The drug absorption is relatively rapid. It usually takes a duration between 1 to 4 hours for the plasma concentration to peak. The elevation of the peak concentration is proportional to the intake dosage. According to previous research on absorption, Nivolumab demonstrates linear pharmacokinetics. The area under the curve (AUC) presents a dose-proportional increase, implying the dose-proportional increase in the bioavailability of administrated Nivolumab. When the distribution of

Nivolumab enters a steady phase, the mean volume of Nivolumab is 6.8L. To evaluate the variability of distribution, previous studies introduce the parameter, coefficient of variation (CV%) for Nivolumab, which reaches 27.3% [3]. It is suggested that liver metabolism facilitates Nivolumab into separate peptides and amino acids. The half-life of Nivolumab inside the patient's body is 25 days, which indicates part of its elimination characteristics. However, the specific elimination route of Nivolumab has not been fully clarified yet.

3. Microenvironment

It is concluded from previous research that the aetiology of HCC affects the immune responses and induces specific microenvironment features [4]. The whole composition of the HCC microenvironment includes complex interactions between immune effector cells, immunodepressant cells, the cytokine milieu, and intrinsic signaling pathways of malignant cells [5]. Before the treatment, immune-related cells such as APCs including macrophages and dendritic cells may express aberrant levels of PD-L1. Immune cells can over-express PD-1 in the tumor microenvironment (TME) as well. The overexpression of PD-1/PD-L1 drives immune exhaustion at the hepatic malignancy that is believed to be dominated by a cytokine milieu with abundant TGF- β and IL-10 [5]. During the exhaustion, the activation of CD4+ helper T cells and cytotoxic T lymphocytes is inhibited. The signaling of the T-cell receptor is suppressed by the PD-1/PD-L1 pathway through the PI3K/AKT pathway, ultimately suppressing T-cell growth and survival [5].

When Nivolumab is administered to a patient with HCC, it will greatly affect the TME. Firstly, it enhances cytotoxicity. More cytotoxic T cells will be activated, which further commences cytotoxicity against hepatic tumor cells. The process is mediated by the T-cell receptors and is antigen-dependent with high specificity. FAS-ligands and IFN- γ secretion are involved in the direct contribution to cell death and suppression of tumor growth, respectively with the initiation from cytotoxic CD8+ T cells. Activated CD4+ T lymphocytes also boost immunity against malignant cells by the production of pro-inflammatory cytokines TH1, which improves the proliferation of cytotoxic T cells. Activated T cells can enhance the secretion of cytotoxic molecules including perforin and granzymes, inducing apoptosis of tumor cells in HCC patients. Elevated production of cytokines contributes to the activation of macrophages for an improved efficiency of antigen presentation. Ultimately, more T lymphocytes are recruited, and the anti-malignancy responses are amplified. Besides the boosting of anti-tumor responses, the intake of Nivolumab also modulates immune suppression. The blockage of the PD-1/PD-L1 pathway downregulates the existence of immunosuppressive cells comprising T regulatory cells and myeloid-derived suppressor cells. As a result, the TME is shifted towards a more immunogenic phase against hepatic tumors.

4. Clinical trials

4.1. CA209-459 Nivolumab V Sorafenib in HCC (2016-2017)

As a research study carried out in the early stage of discoveries on the efficacy of Nivolumab against HCC, this trial was a randomized, multi-center phase 3 study aimed at finding out whether Nivolumab can challenge Sorafenib for the first-line treatment of unresectable, stage BCLC HCC including B7 and Child-Pugh Class A (category 1) [6]. Three aspects of performance, safety, tolerability, and effectiveness are considered for comparisons between Nivolumab and Sorafenib. The surveyed group consists of approximately 726 HCC patients in advanced phases. Three stages, screening, medication, and follow-up are designated to proceed with the whole process. The effective data are as follows: The overall survival has a hazard ratio of 0.85 with a 95% confidence interval between 0.72 and 1.02; $p = 0.0752$. A p -value over 0.05 indicates that the trial did not achieve statistical significance for its pre-specified primary endpoint of overall survival (OS). The median overall survival for the patients treated with Nivolumab is 16.4 months, compared with 14.7 months for the Sorafenib group. Defined as the proportion of patients with a partial or complete response to the therapy, the overall response rate (ORR) directly measures the tumoricidal activities of two drugs: 15% for Nivolumab, and 7% for Sorafenib [5].

As a result, an improved trend toward OS and ORR by Nivolumab over Sorafenib might still be implied in this trial, though the statistical significance of the primary endpoint is not reached. This trial showed promising characteristics of efficacy and safety of Nivolumab, thus indicating more possible choices other than the standard Sorafenib treatment.

4.2. CheckMate 040 and 5-year follow-up (2020, 2024)

This trial is an open-labeled phase 1/2 study recruiting 148 patients. It is characteristic of multicenter and multicohort. Participants are randomized into groups taking three various regimens. In combination with Yervoy (Ipilimumab) for patients with the previous administration of Sorafenib, Nivolumab demonstrated controllable safety, durable responses, and a promising objective response rate (32%) in regimen A and received accelerated approval from the FDA accordingly [7]. In 2024, research following CheckMate 040 focuses on the clinical benefits of Nivolumab monotherapy in Sorafenib-naïve and experienced groups and detects durable benefits and no new safety signals in patients in advanced stages. It also presents a longer overall survival and higher overall response rate with baseline PD-L1 higher than or equal to 1% [8].

4.3. CheckMate 9DW (with results released in 2024)

In this clinical trial, a combinatory drug consisting of Nivolumab and Ipilimumab is compared with Sorafenib or Lenvatinib as the first-line treatment for unresectable hepatocellular carcinoma. This open-label, randomized, phase 3 clinical trial recruited approximately 668 patients without previous systemic therapy. The overall survival of involved patients is defined as the primary endpoint of this trial. Compared with 20.6 months for median OS in standard treatment groups, the combinatory group demonstrated an mOS value of 23.7 months. The two-sided p-value is 0.0180, which indicates statistical significance in the primary endpoint [9].

4.4. A trial of Nivolumab and TACE or TAE for cancer of the liver (TACE 3) (2020-2024)

According to AASLD guidelines, the medication options are divided into curative and noncurative interventions. Transarterial embolization (TAE) or chemoembolization (TACE, including doxorubicin as the chemotherapy drug) is classified as a noncurative, first-line therapy against BCLC stage B HCC by slowing tumor progression. Nivolumab is considered as a subsequent-line therapy upon malignancy progression by AASLD. This randomized, phase 2/3 trial consisting of 522 patients is designated to discover whether Nivolumab combined with TACE or TAE can improve the efficacy of a single treatment by TACE/TAE and further evaluate the side effects and influence on life quality. Blood samples and tissue biopsies are recruited for research purposes, especially for biomarker detection. Although the recruitment has ended, the data has not yet been fully released.

5. Future development and concerns

Many areas including treatment strategies against various stages of hepatocellular carcinoma have not been fully discovered yet. As many clinical trials are underway, there is an emerging significance of the validation of biomarkers for the guidance of clinical decision-making. The targets of validation include Nivolumab, both as a monotherapy and as a combinatory therapy with other medications such as Ipilimumab. Growing concerns also focus on drug resistance against Nivolumab in HCC patients. Some mechanisms have been proposed but comprehensive clarification is still needed. A newly released study suggests the prevention of inflammasome responses by TMEM176A/B that affects the efficacy of the Regorafenib-Nivolumab regimen in early progressors, thus implying potential resistance procedures and developmental targets of novel medication in immunotherapies [10].

6. Conclusion

The early advancements in discoveries of the efficacy of Nivolumab against HCC could be dated back to 2017. As an immune checkpoint inhibitor targeting PD-1, Nivolumab mainly reactivates T lymphocyte-mediated immune responses against hepatic tumor cells and downstream signaling

pathways. The microenvironment inside HCC patients is changed by Nivolumab intake through cytotoxicity enhancement, boosting of immune responses, and regulation of immune suppression, thus improving the prognosis and life qualities of HCC patients. Compared with the strategy of Nivolumab monotherapy, it is implied in previous clinical trials that combinatory therapy including Nivolumab with other medications may have a more promising overall survival of patients with HCC in various stages, no unexpected side effects, and better life qualities during medication. Up to now, HCC is still a tough disease with standard therapy including Sorafenib which is characteristic of unsatisfactory prognosis and tyrosine kinase inhibitor-related adverse effects. Although more research with solid statistical significance is still in need in areas regarding Nivolumab-related treatment against HCC, there have been some promising first results of clinical trials showing its superiority over standard primary medications in overall survival, especially those of some combinatory strategies such as Nivolumab and Ipilimumab.

By combining a series of relatively representative or driving clinical trials that started in 2016, some new trends could be concluded. Firstly, the core of research on Nivolumab-involved treatment against HCC has been transformed from comparisons of monotherapy between Nivolumab and other standard first-line therapies to those between Nivolumab regarding combinatory medications and standard HCC treatment strategies. Secondly, newly updated studies put more effort into the application of Nivolumab-involved treatment in the first line instead of following phases or usage with assisting objectives. Thirdly, the scale of applicable stages of Nivolumab medication has been broadened into phases with a high risk of recurrence after curative hepatic resection or ablation, for example, the undergoing CA209-9DX (NCT03383458), a study of Nivolumab in participants with Hepatocellular Carcinoma and previous curative means. However, the mentioned Nivolumab resistance mechanisms and discoveries from previous trials are brief, thus necessary for future summarization.

Two research directions might be proposed based on completed trials. To begin with, further findings are needed to discover new first-line Nivolumab-involved combinatory immunotherapy against HCC with the aims of elevated overall survival (OS), minimal adverse influence, and improved quality of life. The OS should be maintained as the primary endpoint, whose statistical significance must be achieved. Furthermore, more biomarkers should be recruited to validate the efficacy of Nivolumab-involved treatment of HCC and the acceleration of the cycles of trials.

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