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The Role of PD-1/PD-L1 Inhibitors in the Treatment of Nasopharyngeal Carcinoma in the Epstein-barr Virus Microenvironment

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Abstract. This article offers an extensive examination of nasopharyngeal carcinoma (NPC), with a particular emphasis on its epidemiological features, relationship with Epstein-Barr virus (EBV) infection, classification system, and current immunotherapy approaches. NPC is notably prevalent in East and Southeast Asia, displaying a robust association with EBV infection, particularly in the non-keratinized subtype. Considering the successful implementation of PD-1/PD-L1 immune checkpoint substance across various cancer, their potential therapeutic benefits in NPC have attracted considerable attention. Although PD-1/PD-L1 inhibitors have exhibited effectualness in NPC patients, the response rate remains inconsistent, suggesting a requirement for deeper investigation into the regulatory mechanisms that govern PD-L1 expression. Furthermore, the approach of combined interferon therapy, designed to augment anti-tumor immunity, has demonstrated potential in enhancing therapeutic outcomes and extending patient survival when administered concomitantly with PD-1/PD-L1 inhibitors. However, several obstacles remain, including drug resistance and the substantial heterogeneity observed in NPC tumors. Tumors from different patients display variations in gene expression patterns, immune microenvironment composition, and other factors, which may lead to divergent patient responses to the combined treatment regimen of PD-1/PD-L1 inhibitors and interferon. This article highlights the research significance of PD-1/PD-L1 combined with interferon in NPC treatment and anticipates its extensive clinical application in the future. Nonetheless, to achieve this goal, several challenges must be tackled through persistent and rigorous research and exploration.

Keywords: Nasopharyngeal carcinoma, PD-1/ PD-L1, epstein-barr virus, tumor microenvironment, interferon.

1. Introduction

NPC is a squamous cell tumor originating in the mucosa of the nasopharynx, commonly found in Rosenmuller's fossa. In 2020, the IARC reported 133,354 cases of nasopharyngeal cancer worldwide, accounting for 0.7% of all cancer diagnoses. Interestingly, nasopharyngeal cancers show a significant geographic distribution, with more than 77% of nasopharyngeal cancers occurring in East and Southeast Asia. In Southeast Asia, nasopharyngeal cancer ranks 10th in the overall population [1]. Nasopharyngeal cancer is an epithelial cancer associated with EBV infection. EBV infection promotes tumorigenesis in NPC and forms a complex tumor immune microenvironment (TME) in NPC. In accordance with the WHO classification system, NPC is primarily categorized into three distinct types: keratinizing squamous cell carcinoma, non-keratinizing carcinoma (which encompasses differentiated and undifferentiated subtypes), and basaloid squamous cell carcinoma. Notably, non-keratinizing carcinoma is the most prevalent type, with the undifferentiated non-keratinizing NPC subtype being particularly prominent. A strong correlation exists between non-keratinizing NPC and EBV infection, as evidenced by the fact that nearly all patients diagnosed with undifferentiated or partially differentiated non-keratinizing NPC exhibit detectable levels of EBV. This observation implies that EBV infection may play a pivotal role in the development of this specific type of NPC [2].

PD-1/PD-L1 antibody therapy has demonstrated rapid onset, sustained responses, and favorable tolerability across a wide range of cancers, indicating promising therapeutic efficacy in patients with NPC. Currently, numerous trials are underway to evaluate the effectiveness and feasibility of PD-1/PD-L1 inhibitors as a potential treatment strategy for NPC. The preliminary results have shown encouraging signs, suggesting the potential for further exploration and development in this therapeutic area. The PD-L1/PD-1 pathway in the human body holds potential as a biomarker for immunotherapy effectiveness. However, it is noted that not all patients experience optimal treatment outcomes with PD-L1/PD-L1 antibody therapy. This underscores the importance of conducting further research to optimize treatment strategies and ultimately enhance patient outcomes, emphasizing the need for deeper investigation to improve therapeutic approaches and patient prognosis.

PD-1 and PD-L1 molecules are key components of the immune system, functioning to suppress T cell activity within the TME, thereby helping tumor cells evade attack by the immune system. Combined with interferon therapy can further enhance the anti-tumor activity of the immune system, and improve the body's ability to recognize and kill nasopharyngeal carcinoma cells by interfering with viral replication, promoting the proliferation and activation of immune cells and other mechanisms. Previous studies have shown that PD-1 inhibitor combined with chemotherapy has achieved significant efficacy in the treatment of nasopharyngeal carcinoma, which can control tumor growth and reduce tumor volume. Combined interferon therapy is expected to further improve the tumor control rate and extend the progression-free survival (PFS) and overall survival (OS) of patients. The study of PD-1 and PD-L1 combined with interferon in the treatment of nasopharyngeal carcinoma It can not only improve the therapeutic effect, expand the therapeutic indication, promote the development of immunotherapy, but also improve the quality of life of patients. In the future, with the deepening of research and accumulation of clinical practice, this combination therapy is expected to play a greater role in the treatment of nasopharyngeal cancer.

2. Therapeutic Potential of PD-1/PD-L1 Inhibitors

Following surgery, chemotherapy and radiotherapy, immunotherapy has emerged as a new and effective strategy for treating human cancer. Previous studies have shown that the increased expression of PD-L1 in tumor cells and its expression in the microenvironment is associated with the presence of EBV in DLBCL (diffuse large B-cell lymphoma). In addition, the PD-1 blocker (nabuliumab) can enhance the cytotoxic effects of IFN-β-activated NK (natural killer) cells in

NPC cells through a TRAIL-mediated mechanism. The inhibition of the PD-1/PD-L1 interaction holds a pivotal position in cancer treatment, primarily through the restoration of suppressed immune system functionality and the augmentation of the body's immune response towards tumors. Notably, tumors such as renal cell carcinoma and non-small cell lung cancer frequently demonstrate elevated PD-L1 expression levels. This characteristic renders patients with nasopharyngeal carcinoma as potential candidates who may benefit from PD-1/PD-L1 antibody therapy [3,4]. In NPC, immune checkpoint proteins, particularly PD-L1 , are closely associated with both the TME and the endemic nature of the disease. These proteins play a pivotal role in the onset and progression of nasopharyngeal carcinoma, exhibiting a strong correlation with tumor immune evasion and treatment outcomes. PD-L1, in particular, is abundantly expressed within NPC tumors and engages with immune cells in the TME, ultimately inhibiting T-cell activity and facilitating the evasion of tumor cells from immune system assaults. Furthermore, other immune checkpoint proteins, including B7-H4 and IDO-1, are also present in nasopharyngeal carcinoma and actively involved in modulating the tumor's immune responses. Due to the high sensitivity and specificity of plasma EBV-DNA, it can be used as an important marker for early diagnosis of nasopharyngeal carcinoma [5]. It has been reported that PD-L1 is frequently expressed in extranodal NK/T cell lymphomas, and Various studies have demonstrated disparities in the understanding of PD-L1 (programmed death-ligand 1) positivity and its prognostic implications. For example, in the context of melanoma, PD-L1 expression is typically elevated and exhibits a strong correlation with the efficacy of immunotherapy. Elevated TPS (tumor proportion score) or CPS (combined positive score) indicating PD-L1 expression has been established as a beneficial predictor of immunotherapy response, thus reinforcing the prognostic relevance of PD-L1 positivity. Nonetheless, the precise mechanisms that underlie PD-L1 positivity and prognosis may differ among different tumor types and are subject to the influence of numerous factors. Consequently, in

clinical practice, it is imperative to undertake a thorough evaluation, taking into account the unique circumstances of patients and a multitude of biomarkers, in order to formulate individualized treatment strategies [6].

2.1. Mechanism of Action

PD-1, as a receptor with immunosuppressive properties, is primarily expressed on the exterior of T cells. In contrast, PD-L1 has a broader distribution and is present on the surface of various cells, including tumor cells. When PD-1 specifically binds to PD-L1, it further transmits inhibitory signals, which ultimately have a significant impact on the functional state of T cells, potentially involving the suppression or regulation of cellular functions. When T cells are reactivated, they are able to recognize and attack tumor cells more efficiently. These include the induction of apoptosis of tumor cells by releasing cytokines such as interferon, tumor necrosis factor, etc., and the direct killing of tumor cells by cytotoxic effects. The binding of PD-1 and PD-L1 molecules leads to T-cell dysfunction and exhaustion and immune tolerance in the TME. The focus of new immunotherapies for the treatment of cancer is to shift the balance from the pro-TME to the anti-TME [7].

2.2. Application Status of Inhibitors

Recently, amidst the swift advancements of tumor immunotherapy, the market size of PD-1 and PD-L1 inhibitors has achieved significant and rapid growth. PD-1 and PD-L1 inhibitors have gradually become important options for the remedy of an array of cancers. At present, a number of PD-1 inhibitors have been marketed.Recently, PD-1 and PD-L1 inhibitors have demonstrated remarkable effectiveness in the management of nasopharyngeal carcinoma, showcasing their therapeutic potential. For example, PD-1 inhibitors such as toripalimab and camrelizumab have achieved positive results in clinical trials of NPC, significantly improving the PFS and OS of patients. PD-1 inhibitors are often used in combination with chemotherapy drugs to form a combination treatment regimen. Toripalimab combined with gemcitabine and cisplatin (GP) has made a breakthrough in the treatment of nasopharyngeal carcinoma and significantly improved the prognosis of patients. Due to the excellent performance of PD-1 inhibitors in the treatment of nasopharyngeal carcinoma, its combination therapy has been included in the Chinese Society of Clinical Oncology (CSCO) guidelines for the diagnosis and treatment of nasopharyngeal carcinoma, and has become an important choice for the treatment of nasopharyngeal carcinoma. In addition, with the deepening of research, the indications of PD-1 inhibitors are also expanding, providing treatment options for more tumor patients.

3. Interferon Binding

EBV DNA negativity in NPC signifies the absence of detectable EB virus DNA in the patient's sample or an extremely low viral load beneath the detection threshold. This typically implies that the tumor's genesis may not be directly linked to the EB virus or that the virus is in a minimally active state. Conversely, EBV DNA positivity in NPC signifies the detection of EB virus DNA in the patient's sample, indicating a potential significant role of the EB virus in the tumorigenesis and progression, alongside active viral replication within the body. Research indicates that EBV DNA-positive NPC tumor cells may demonstrate reduced differentiation capacity, enhanced stem cell properties, and upregulated signaling pathways associated with cancer markers [8]. These attributes may be associated with EB virus infection, given the virus's capacity to drive the expression of specific genes and facilitate cellular transformation. In the multicellular milieu of nasopharyngeal carcinoma, a comprehensive upregulation of interferon response has been noted, suggesting immune system activation in response to the presence of nasopharyngeal carcinoma [9,10]. According to previous studies, the specific pattern of MDA5 (Melanoma Differentiation-Associated Gene 5) released by IFN is most suitable for CD8+T cell priming, and researchers are exploiting this principle for cancer immunotherapy [11]. Interferon therapy, specifically utilizing agents like IFN-α, when combined with anti-PD-1 treatment, has demonstrated notable antitumor efficacy across diverse mouse tumor models. This therapeutic combination is capable of substantially augmenting the antitumor immune response, impeding tumor progression, and extending the overall survival duration of mice. In the context of a mouse model of hepatocellular carcinoma, administration of polyethylene glycol-conjugated interferon α (PEG IFNα) alongside anti-PD-1 antibody led to significant attenuation of tumor growth, prolongation of overall mouse survival, and diminution in the number of lung metastases. Furthermore, a marked elevation in the infiltration of CD8+ T cells was observed within the tumors of mice that received the combination treatment, accompanied by an enhancement in the cytotoxic capabilities of these T cells. These empirical findings suggest that the combination therapy involving interferon α and anti-PD-1 antibody manifests substantial antitumor activity in the mouse model of liver cancer, thereby offering a novel approach and direction for immunotherapy in clinical tumor management [12].

3.1. Safety

The controllability of interferon therapy in NPC treatment is generally manageable, albeit with the presence of side effects. Commonly encountered adverse reactions encompass fatigue, anorexia, nausea, vomiting, and leukopenia. A substantial portion of these adverse reactions can be effectively managed and mitigated through appropriate medical interventions and supportive care. Nonetheless, it is important to note that interferon therapy may also precipitate severe side effects, particularly depression and suicidal ideation, especially when administered in long-term or high-dosage regimens. An illustrative case from the NPC-2003-GP OH study involves a male adolescent patient who committed suicide 8 months after the cessation of IFN-β treatment, preceded by sleep disturbances as a reported side effect. Therefore, it is imperative to conduct rigorous monitoring of patients' physical and psychological conditions during the course of treatment and promptly adjust the treatment plan as necessary to ensure the safety of the patient [13]. In nasopharyngeal carcinoma, a synergistic interplay is observed between IFN-γ and ULBP3, a component of the EBV, in the collective modulation of PD-L1 expression. Specifically, EBV infection of nasopharyngeal carcinoma cells in a controlled laboratory environment has the capacity to elicit an upregulation of PD-L1, and this upregulation process is further augmented in a synergistic manner by the presence of IFN-γ [14]. The combination of interferon and PD-1 may lead to excessive activation of the immune system and trigger autoimmune reactions, such as immune reaction hepatitis and autoimmune thyroid disease. These reactions may aggravate the patient's condition or trigger new diseases. Moreover, there may be drug-drug interactions between interferon and PD-1 monoclonal antibody, which may affect the metabolism and efficacy of drugs. In addition, patients may also receive other drug therapies, such as chemotherapy and radiotherapy, which may also interact with interferon and PD-1 monoclonal antibodies. Although combination therapy with interferon and PD-1 may improve antitumor efficacy, patients may still be at risk for drug resistance and recurrence. This may be related to factors such as the heterogeneity of tumor cells, the complexity of microenvironment, and individual differences in patients. Therefore, even though interferon, as an endogenous regulatory factor secreted by immune cells, has been used in clinical practice for decades, its safety and application value in the field of virus prevention and treatment, immune regulation and other fields have been fully affirmed. However, due to its wide range of effects and diverse patterns, the anti-tumor efficacy of single agent is poor, but its safety is still an important consideration in the combination therapy. Clinical evidence suggests that monotherapy with PD-1 inhibitors demonstrates a restricted therapeutic impact on patients diagnosed with NPC [15]. Moreover, NPC is a tumor dominated by EB virus, and its pathogenesis and TME are different from most tumors. Therefore, how to improve the efficacy of interferon combined with PD-1 and PD-L1 monoclonal antibodies while ensuring safety is still a problem to be explored.

3.2. Development Potential of Combination Therapy

Many studies have demonstrated the possibility of interferon combined with PD-1 antibody in the remedy of tumors. For example, the study of Professor Qin Lunxiu and Dong Qiongzhu's team in Fudan University showed that long-acting pegylated interferon α (PEG-IFNα) as an adjuvant drug combined with PD-1 antibody has a significant synergistic effect in the treatment of hepatocellular carcinoma. This study revealed that PEG-IFNα enhanced the efficacy of PD-1 by modulating tumor immune responses and enhancing CD8+T cell infiltration and function. The effectiveness of combinatorial therapeutic approaches for NPC remains constrained. Studies have revealed that IFNβ is capable of augmenting the cytotoxic capabilities of NK cells specifically against NPC, and this effect is further exacerbated by the blockade of PD-1. Research investigations have indicated that IFN-γ, which is secreted by CD8+ T cells, NK cells, and NKT cells, plays a substantial role in the stimulation of PD-L1 expression. Simultaneously, IFN-γ is also implicated in the downregulation of ULBP3 within NPC cells, potentially influencing the immune-mediated eradication of these cells.[16] It is noteworthy that PD-L1 exhibits overexpression in EBV-positive NPC, and CD8+ T cells extracted from samples with positive EBV DNA serum levels exhibit an elevated immune response, hinting at a potentially enhanced responsiveness to anti-PD-1 therapeutic interventions. Consequently, the reversal of CD8+ T cell exhaustion and the enhancement of immunotherapy efficacy are of utmost importance. Elevated IFN responses are observable in NPC cells with positive EBV DNA serum levels, and these responses are of critical significance in regulating immune functions pertinent to cancer [17]. Interferon can activate CD8+T cells and make them enter a proliferative state, thereby enhancing the immune response and enhancing the cytotoxic effect of CD8+T cells, so that they can more effectively recognize and kill infected cells or tumor cells. Therefore, it can be concluded from the above study results that PD-1/PD-L1 inhibitors combined with interferon have application potential in the treatment of NPC, and further trials/studies are needed to evaluate this study.

4. Conclusion

This article primarily compiles recent applications and experimental outcomes of immunotherapy in NPC to derive pertinent insights. A positive correlation exists between PD-L1 expression and EBV infection in the context of NPC. The elevated expression of PD-L1 may be associated with T-cell exhaustion and compromised immune function, which holds particular significance in the context of EBV infection. The amalgamation of anti-PD-1/PD-L1 immunotherapy with other therapeutic modalities, including interferon, chemotherapy, and radiotherapy, has exhibited certain positive effects in NPC treatment. Consequently, the blend of interferon with PD-1/PD-L1 inhibitors is anticipated to be efficacious in NPC therapy. The research background and significance of interferon combined with PD-1/PD-L1 antibodies in tumor treatment are underscored by their notable synergistic effects, inhibition of tumor volume and metastasis, remodeling of the tumor microenvironment (TME), and capability to prevent tumor recurrence. This article also consolidates related articles and experimental results of interferon combined with PD-1/PD-L1 antibodies in treating other tumor types, aiming to gain insights for future combinations of different interferon types with PD-1/PD-L1 antibodies. However, this report lacks an adequate analysis of the disparities between positive and negative NPC due to the significant differences in PD-L1 overexpression between EBV-positive and EBV-negative NPC, which impacts the choice of treatment strategy. Furthermore, the selection of interferon type, drug resistance, and the high heterogeneity of NPC tumors were not thoroughly analyzed, and these aspects require further attention in future research. In the future, through comprehensive investigation of the regulatory mechanisms of PD-L1 expression and utilization of PD-1/PD-L1 inhibitors, the immune microenvironment, including ULBP3, may be further elucidated.

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