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Clinical Evidence and Prognostic Mechanisms of Perioperative Immune Combination Therapy for Hepatocellular Carcinoma

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Abstract. Hepatocellular carcinoma (HCC) represents a significant leading cause of cancer mortality the worldwide, characterized by a 70% recurrence rate within five years following surgical resection, while conventional adjuvant treatments exhibit limited clinical benefits. This paper extensively evaluates the empirical evidence regarding perioperative integrated immunotherapy in operable HCC, exploring cytokine-mediated prognostic regulatory mechanisms, clinical contributions and practical applications. Initially, the paper organizes primary clinical trial findings concerning local-regional interventions and immunotherapy, specifically highlighting perioperative combined regimens like the EMERALD-1, NEO-LAP and IMBRAVO-050. Subsequently, it is defined primary prognostic pathways, including tumor microenvironment restructuring, minimal residual disease eradication, and the synergistic interaction between anti-angiogenic agents and immunotherapy. Furthermore, current clinical practice gaps include optimal timing of intervention and specific therapeutic combinations. This work provides a structured framework for implementing standardized perioperative immune-based strategies in HCC treatment, while simultaneously providing strategic guidance for the subsequent investigations focusing on both clinical and mechanistic dimensions.

Keywords: Hepatocellular carcinoma, perioperative period, immune combination therapy, prognostic regulatory mechanism, clinical evidence

1. Introduction

Liver cancer ranks among the top three types of malignant tumours globally and has been ranked as the sixth most common type of malignant disease in China for several years running [1]. Approximately 75%-85 percent of primary liver cancer cases are hepatocellular carcinomas. The incidence and mortality have been on the rise across many areas owing to long-term infection with the hepatitis B virus, metabolism-related steatohepatitis, alcohol consumption, etc. Although the surgical excision of early-stage hepatocellular carcinoma cells may be highly curative currently, due to poor recurrence effects after treatment, it cannot be considered an absolute success criterion at present. More than seven-tenths of patients developed recurrences in the following five years after undergoing radical surgery. Therefore, most patients with liver cancer ultimately died of this disease

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[2]. In recent years, conventional adjuvant strategies for cancer prevention after surgery have shown limited efficacy, such as chemotherapy and targeted therapies combined with some traditional immunostimulant agents. STORM showed no difference in recurrence-free survival and overall survival between adjuvant sorafenib and placebo after curative resection or ablation therapy; therefore, it is imperative to find a better strategy for the adjuvant treatment stage [3].

Over the past 10 years, the emergence of immune checkpoint inhibitors (ICIs) has transformed the systemic therapy of advanced hepatocellular carcinoma. The immune checkpoint pathways, particularly the programmed cell death protein-1 (PD1)/programmed death ligand-1 (PDL1) axis and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) pathway, are responsible for tumour immune evasion and inhibit antitumour immunity. Through pathway blockades, endogenous anti-tumour immune activity of the body can be restored and reactivated, achieving long-term remission in some cases. The Phase III IMbrave150 trial showed that azezolimumab (antipDIL)) combined with bevacizumab (anti-Vascular Endothelial Growth Factor A: anti-VEGF)) was the first-line standard of care for unresectable hepatocellular carcinoma; compared to sorafenib, it showed better Progression-Free Survival and Overall Survival [2]. This successful case has brought about changes in clinical application and also prompted more research into the use of immunotherapy at an early stage for resectable hepatocellular carcinoma (HCC) during the perioperative period.

Both biological bases and clinical applications for using immunotherapy in the perioperative period are valid. Surgical resection itself causes a systemic inflammatory response and immunosuppression due to surgical stress, tissue damage and anesthetic-related factors. This could enhance the stability of minimal residual disease (MRD) and circulating tumour cells (CTC) [4]. Thus, during the operation, it is necessary to create conditions more conducive to activating anticancer immunity to eliminate microscopic metastatic foci and prevent recurrence. In addition, due to its role in immunoselection, the liver is regarded as an immunotolerant organ. There are abundant immunosuppressive cells within the sinusoid network of blood vessels, and inhibitory cytokines can also be produced. Neoadjuvant immunotherapy reduces tumor burden before surgery, achieves downstaging to remove small micrometastases early, and induces systemic immune memory through preoperative immune stimulation, laying a foundation for postoperative therapy. Moreover, adjuvant immunotherapy targets MRD to extend the survival of patients who have undergone surgery. Combinedly, these rationales help realize the clinical application prospects of perioperative immune-combination therapies for improving patient outcomes after resection in HCC patients.

2. Clinical evidence of perioperative immunotherapy combination strategies

The clinical progress of perioperative immunotherapy for HCC has gone from monotherapies of immune checkpoint inhibitors (ICIs) to rational combinations: combining with anti-angiogenic target drugs, localised treatments such as ablation or radiofrequency thermotherapy; Combining multiple modalities. These strategies overcome tumor-induced immunosuppression to enhance the anti-tumor effect, reduce the postoperative recurrence rate of tumors, and extend patients' overall lifespans. Multiple clinical trials and a series of real-world studies have shown that the application effect is relatively reliable so far [5].

2.1. Local regional therapy combined with immunotherapy

Local regional therapies such as Transarterial Chemo-embolisation (TACE) and Transarterial Radio-embolisation (TARE) have been employed extensively postoperatively to reduce tumour burden or

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recurrence risks for a considerable time. During this time, locoregional treatments have induced immune cell death by immunogenic killing; released tumour-associated antigens, and reshaped the TME to help ICIs work more effectively. Phase III EMERALD1 evaluated the effectiveness and side effects of combining durvalumab with conventional transarterial chemoembolisation (TACE) versus TACE alone for treating unresectable hepatocellular carcinoma (HCC). Although EMERALD1 focused on unresectable HCC, these findings indicate that the addition of an on-tumour-local immunotherapy strategy can improve patients' Progression-Free Survival (PFS) and overall survival when used in combination. Logically extending this idea, it can be reasonably applied in the perioperative management of resectable HCC patients with large tumours, multiple sites, and a high risk of intrahepatic recurrence. For patients with borderline resectable HCC, TACE or ablation combined with ICI might act as a bridge for R0-level reoperation to reduce postoperative tumour dissemination [6].

2.2. Neoadjuvant immunotherapy combinations

Neoadjuvant immunotherapy combinations show good efficacy in surgically resectable HCC. Phase II NEOLAP trials evaluated lenvatinib (a multi-kinase inhibitor with anti-angiogenic and immunomodulatory effects) plus an anti-PD1 antibody for neoadjuvant therapy of unresectable liver cancer to evaluate its efficacy. There were about 40% of major pathological reactions (MPR), among which the treatment-related adverse events could be managed well. These results indicated that neoadjuvant immunotherapy plus targeted therapy is feasible, safe, and biologically active in resectable HCC [7]. Pathological responses to neoadjuvant immunotherapy have been strongly linked to an increase in recurrence-free survival; thus, neoadjuvant- immunotherapy could eliminate viable cancer cells more efficiently and eradicate M.R.Ds before the operation. A prospective phase-II study also revealed favorable toxicities and high patient compliance in the group undergoing combination therapy with Tislelizumab (antiproliferative agent) and Lenvatinib; therefore, it provides a basis for subsequent Phase-III trials.

2.3. Adjuvant immunotherapy combinations

As of now, the most clear-cut clinical evidence is for adjuvant immunotherapy after curative resections or ablations. Phase III, randomised, open-label IMbrave050 Trial: compared the adjuvant treatment of atezolimab + bevacizumab with conventional observation for patients with high-risk HBV-infected hepatocellular carcinoma after curative resection/ablation [8]. High-risk features included macrovascular invasion, microvascular invasion, multiple tumors, large tumor diameter, or elevated alpha-fetoprotein. The first Endpoint is recurrence-free Survival (RFS). The Results show that Adjuvant Atezolumab Plus Bevacizumab can extend RFS (Relapse-Free Survival) and reduce recurrence risks compared to the active control group. The safety profile is consistent with that of the IMbrave150 trial; there have been no new or unforeseen adverse reactions. IMBrave050 has been a benchmark study demonstrating immune-combination therapy as a new standard of care in adjuvant treatment for high-risk liver cancer patients and closing the long-standing effectiveness gap of an effective adjuvant therapy [8].

There are some patients' responses to perioperative-immune therapies in terms of efficacy. Several retrospective cohort studies in China, Europe and the USA have shown that perioperative PD1/PDL-1 inhibitor combination therapy, coupled with targeted therapy or localised therapies, had a lower recurrence rate, longer RFS (recurrence-free survival), and a favourable safety profile than those using surgery as monotherapy or undergoing conventional adjuvant treatment. Real-world

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Studies have selection biases and retrospective designs; however, they reflect clinical application situations and help ensure the generalisability of data derived from control trial studies. The obtained data from phases II and III of the pre-operative combination treatment study targeting resectable HCC with immunotherapy suggests that it is both effective, practical and safe in various patient subgroups deemed high-risk based on previous research.

3. Mechanistic insights and prognostic regulatory biomarkers

Perioperative immunotherapy combinations exert therapeutic effects based on coordinated biological effects, including restoring anti-cancer immune responses, remodeling the tumour microenvironment (TME), clearing minimal residual disease (MRD), and preventing cancer recurrence after surgery. Clarifying these mechanisms is crucial for optimizing treatment strategies, identifying predictive biomarkers of response, and eliminating drug resistance.

At the cell level, neoadjuvant immunotherapy combination treatment induces strong activation and clonogenic proliferation of tumour-infiltrating lymphocytes (TILs) with a predominance of CD8-positive cytotoxic T-cells as primary effectors against tumours. TIL density and function show significant changes with disease evolution and are positively correlated with better prognosis. Moreover, ICIs increase antigen uptake and presentation by DCs to prime naïve T cells for proliferation and differentiation into effectors or memory T cell subsets. Immune system response can eliminate both primary cancer and multiple remote metastases simultaneously; establishing a lasting immune memory after surgery to prevent recurrence of the disease.

Clearing MRD can serve as a bridge to achieve lower recurrence after perioperative immunotherapy. Circulating tumour DNA (ctDNA) is highly specific and non-invasive in the assessment of MRD; several studies have shown that high levels of positive ctDNA in patients following liver cancer resection predict a significantly poorer prognosis [9]. Perioperative immunotherapy combinations can substantially reduce ctDNA concentration or convert ctDNA positivity to negativity by eliminating minimal residual disease (MRD) [9]. Patients who showed ctDNA clearance after neoadjuvant or adjuvant treatment had a better prognosis compared to those in whom it remained positive. Therefore, ctDNA is closely related to the prognosis of patients receiving perioperative immunotherapy and should be used in follow-up monitoring.

TME acts as the main mediator of immune response or rejection after immunotherapies. HCC usually has an immunosuppressive TME with high infiltration of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), tumour-associated macrophages (TAMs) and increased levels of inhibitory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGFβ) [6]. Perioperative immunotherapy can reverse the immunosuppressive environment of the TME by decreasing the frequency and regulatory functions of Tregs and MDSCs; promoting a transition from M2 to M1 polarisation of TAMs, thereby increasing pro-inflammatory cytokine production. The above-modified environments offer favorable immune niches that promote anti-tumor immunity and inhibit tumor relapse.

Angiogenesis inhibitors and immunotherapy jointly stabilise the vessel network and activate immunity. Over-expression of VEGF in HCC results in abnormal, tortuous and high-permeability tumour vessels, which inhibit immune cell infiltration and enhance hypoxia-IMDS (immune-mediated disorder) conditions. Anti-VEGF drugs, including bevacizumab and lenvatinib; they adjust the tumour vessels' structure to reduce hypoxia environment and promote the infiltration of immune cells into the cancer microenvironment [1]. Revascularisation improves tumour growth factor levels and enhances the antitumour efficacy of immunoediting by increasing immune checkpoint ligand

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expression. Atezolizumab combined with Bev and PD-1 inhibitors + Lenvatinib in advanced and preoperatively has also demonstrated that this immune angiogenic synergism is crucial.

Molecular profiling has identified several potential genomic and transcriptomic biomarkers of response to perioperative immunotherapy. HCC is also linked to an elevated tumor mutation burden (TMB) and increased expressions of IFN-γ-related genes, PD-L1 status and immune cell infiltration patterns showing more pronounced responsiveness to ICIs across various malignancies [3]. However, these biomarkers have not been fully verified in the perioperative period; no one is regularly applied clinically. In the future, validation and standardisation of these prediction-related indices for guiding patients' needs further study.

4. Synthesis, clinical value and future research direction

Considering the existing clinical and theoretical support for post-operative immunotherapy combinatorial to be a fundamental therapy plan for individuals afflicted by intermediate-or high-intermediate-resectability resected hepatocellular carcinomas. The patients that can gain more benefits are those with larger tumours, multiple locations, micro vessels or macro vessels' invasion; they have increased alpha-fetoprotein values, and other indicators of higher recurrence risk. In comparison to historical adjuvant therapy of sorafenib, perioperative immune-combined regimen shows a better effect on suppressing recurrence and prolonging disease-free survival (DFS), having an acceptable safety profile [10].

Although considerable progress has been made recently, several issues remain unresolved. The optimal timing and order of neoadjuvant or adjuvant immunotherapy are still unclear. Neoadjuvant therapy can eliminate micrometastases earlier and assess treatment response more accurately, while adjuvant therapy specifically targets MRD post-surgery directly. Several ongoing trials are comparing neoadjuvant, adjuvant, and neoadjuvant-adjuvant sequential approaches in their design. The optimisation of the duration of adjuvant immunotherapies also remains unsolved. IMbrave050 used a 1-year course in the trial, and whether a course shorter or longer than one year is equally beneficial remains unclear. The optimal combination partner of ICI in the perioperative period is still being studied, including combinations with anti-angiogenic drugs, local therapy, chemotherapeutic regimens, and novel immunosuppressive agents [10].

Most of the current clinical data come from phase-II trial studies with small sample sizes and short durations, lacking systematic long-term follow-ups. IMbrave050 has provided sufficient upper limit Grade-phase-III data for adjuvant treatment; large, randomly controlled phase-III study periods that extend beyond the initial period should be established to validate mortality-reduction impacts, assess diverse efficacy and side-effect differences, etc. Furthermore, it is still necessary to establish a more realistic research environment simulating various patients with different ages, comorbidities, and disease severities.

It is essential to define and categorize existing norms to maintain uniformity in studies and interventions. Neoadjuvant therapy before surgery aims to reduce tumour size, improve recurrence-free survival, and eliminate micrometastases in patients with initially unresectable tumours. Postoperative adjuvant therapy focuses on MRD detection and elimination after resection or ablation failure. Conversion therapy is performed on initially unresectable patients to make them re-eligible for surgery. These three purposes are distinct, and the target patient populations for each also vary significantly.

Future research directions of perioperative HCC immunotherapy are diverse. Firstly, biomarker-guided personalised treatment will become the core direction, including ctDNA-based therapy adjustments, PD-L1 expression levels, TMB indicators, IFN-γ signatures, and TME immune-cell

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profiles. Secondly, novel rational combination regimens of ICI with cancer vaccines, oncolytic viruses, or epigenetic inhibitors such as ALK inhibitors (e.g., Crizotinib) will also be constructed. Thirdly, perioperative immunotherapy will be applied to more populations, including those who have undergone liver transplantation, intermediate-stage HCC patients at different stages, and pediatric or younger adult patients. Fourth, strategies to overcome immune resistance include the active exploration of targets for inhibiting Tregs, MDSCs, IDO, TGF-β, and other immunosuppressive pathways. Finally, health economics and quality-of-life studies will help optimize the value and accessibility of perioperative immunotherapy in the global healthcare system.

5. Conclusion

Perioperative immune-combination therapy represents a significant advancement in the comprehensive management of resectable HCC, providing a novel and highly effective approach to diminish post-surgical recurrence and improve long-term clinical results for individuals with this condition. This paper extensively gathers and synthesizes clinical data regarding perioperative immune combination strategies for HCC. It is evident that the IMbraimeo050 trial established the landmark importance of adjuvant immune combination therapies within the standard of care for high-risk resectable HCC, while also validating the practicality and efficiency of neoadjuvant protocols through the neo-lap approach. A profound insight into the primary regulatory mechanisms governing the activation of Tumor-Infiltrating Lymphocytes, the management of Minimal Residual Disease, modifications in the Anti-tumor Immune Suppressive Tumor Environment, and the synergistic impact of anti-angiogenic and Immune Checkpoint Inhibitor therapies is achieved. Simultaneously, it clarifies the conventional definitions of neoadjuvant, adjuvant, and conversion therapies in clinical settings, and compiles the main disputes concerning the optimal timing for selecting a specific modality. By utilizing higher-grade clinical evidence and mechanistic insights as the foundation for evaluating how to implement peri-operative immune combination therapy for HCC patients. It also facilitates the establishment of a framework for subsequent clinical trial research. Nevertheless, certain constraints exist within this review, as the majority of evidence originates from phase II trials with limited patient numbers and no direct head-to-head large phase 3 comparisons. Future endeavors should involve conducting a single randomized controlled trial across multiple centers, while searching for specific biomarkers for validation and treatment prediction, which might lead to personalized peri-operative immunotherapies that are more precisely directed toward a broader spectrum of HCC patients.

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