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Advances in Systemic Therapy for Advanced Hepatocellular Carcinoma: Paradigm Evolution from Single-Agent Chemotherapy to Targeted Therapy Combined with Immunotherapy

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Abstract

Primary liver cancer, particularly hepatocellular carcinoma (HCC), represents a significant global public health burden with persistently high incidence and mortality rates. The systemic treatment of advanced HCC has undergone a paradigm evolution from traditional cytotoxic chemotherapy to molecular targeted therapy, and now to the current era centered on the combination of targeted therapy and immunotherapy. Traditional chemotherapy has shown limited efficacy due to tumor insensitivity and substantial toxicity. Since the approval of sorafenib in 2007, the era of targeted therapy began; however, the efficacy of single-agent targeted therapy has encountered bottlenecks. In recent years, the introduction of immune checkpoint inhibitors has brought breakthroughs. Notably, the “targeted plus immunotherapy” regimen represented by atezolizumab combined with bevacizumab (IMbrave150 study) and the “dual immunotherapy” regimen represented by durvalumab combined with tremelimumab (HIMALAYA study) have been established as new first-line standards for advanced HCC. These approaches have significantly improved objective response rates and overall survival in patients and have been recommended as the highest-level evidence in major clinical guidelines. This article systematically reviews the developmental trajectory of systemic therapy for HCC, comparatively analyzes the efficacy, safety, and applicable populations of key drugs across different eras, and discusses the current challenges facing combination strategies, including drug resistance and biomarker screening. The conclusion highlights that the transition from monotherapy to combination therapy marks the entry of HCC treatment into a new stage characterized by synergistic enhancement, diversified regimens, and a commitment to improving patient prognosis. Future directions will focus on overcoming drug resistance, exploring novel drug combinations (such as antibody-drug conjugates), and achieving more precise individualized treatment through biomarkers.

Keywords

liver cancer, targeted therapy, immunotherapy, IMbrave150, HIMALAYA

1. Introduction

According to data released by the National Cancer Center of China, in 2022, there were 367,700 new cases of primary liver cancer nationwide, ranking fourth among all cancers (after lung cancer, colorectal cancer, and thyroid cancer) [1]. The incidence rate ranked fifth (after lung cancer, female breast cancer, thyroid cancer, and colorectal cancer). In the same year, 316,500 deaths were attributed to primary liver cancer, with both the number and rate of deaths ranking second (after lung cancer) [2]. It is estimated that by 2040, the number of new cases will reach 1.4 million and deaths will rise to 1.3 million, representing increases of 55.7% and 57.6%, respectively, compared with current levels. The large population base has kept the incidence of liver cancer at a relatively high level, and this upward trend is expected to continue in the future.

Early systemic treatment primarily relied on cytotoxic chemotherapeutic agents. However, due to their poor efficacy and significant adverse effects, they failed to substantially improve patient prognosis [3]. Since the approval of sorafenib in 2007, systemic therapy for liver cancer entered the molecular targeted therapy era. Since 2017, combination treatment models centered on immune checkpoint inhibitors have broken through the bottleneck of first-line therapy for advanced HCC by virtue of their synergistic mechanisms, marking the formal entry of systemic therapy into a new stage of "targeted therapy combined with immunotherapy."

Against this background, this article aims to systematically review the drug landscape, combination treatment strategies, and cutting-edge development trends in systemic therapy for liver cancer, and to explore possible future directions for drug development. While most recent reviews have discussed targeted therapy and immunotherapy separately, this article integrates them from the perspective of combination strategies in order to provide a different analytical viewpoint. By comparing the efficacy, safety, and differences in applicable populations across various first-line regimens, this review seeks to enhance medication safety and provide reference for optimizing precision treatment strategies and clinical research in liver cancer.

2. Literature Review

Prior to the era of targeted therapy, systemic treatment of liver cancer primarily relied on chemotherapeutic agents (such as 5-fluorouracil and doxorubicin) [4]. However, these agents generally exhibited low sensitivity, with response rates typically below 20% [5]. During this period, strategies such as combination chemotherapy and hepatic arterial infusion were explored, laying the foundation for the subsequent concept of combination therapy. The approval of sorafenib in 2007 marked the entry of liver cancer treatment into the targeted therapy era. For a considerable period, sorafenib remained the only approved targeted agent for advanced hepatocellular carcinoma (HCC). Subsequent single-agent targeted therapies failed to surpass the efficacy of sorafenib, highlighting the limitations of monotherapy and driving the exploration of combination regimens and biomarkers. In recent years, the treatment landscape has entered a new era centered on combination therapy, primarily encompassing two strategies: targeted agents combined with immune checkpoint inhibitors, and dual immune checkpoint inhibitor combinations. The underlying principle is synergistic enhancement: anti-angiogenic targeted drugs can improve the tumor immune microenvironment and enhance immune cell infiltration, while immune checkpoint inhibitors activate anti-tumor immune responses. The combination of the two aims to achieve synergistic efficacy.

2.1 Limitations and Explorations in the Traditional Chemotherapy Era

Chemotherapeutic agents were mainly used in patients with advanced liver cancer [5]. Because HCC is not a chemotherapy-sensitive tumor, systemic chemotherapy has rarely been effective for advanced HCC, with objective response rates generally less than 20%. Even during the period when single-agent chemotherapy was dominant, clinicians began exploring combination strategies to improve efficacy. For example, the Leung regimen (combining cisplatin, doxorubicin, 5-fluorouracil, and α-interferon) increased the partial response rate to 26%. In addition, improvements in local delivery methods such as hepatic arterial infusion chemotherapy and transarterial chemoembolization can be regarded as "combination of administration routes" or "combination of embolization and chemotherapy." These approaches aimed to increase local drug concentrations while reducing systemic toxicity. Such explorations laid the groundwork for the subsequent establishment of the new paradigm of "targeted-immunotherapy combination" [6].

2.2 Breakthroughs in the Targeted Therapy Era

Sorafenib was the first targeted agent approved for first-line treatment of advanced HCC [7]. It exerts anti-tumor effects through multi-target inhibition, blocking both Raf-mediated cell proliferation signaling and VEGFR-mediated tumor angiogenesis. A pivotal Phase III clinical study by Llovet et al. in 2009 [8] confirmed the favorable efficacy of sorafenib, demonstrating that it could effectively prolong overall survival in patients with HCC. Compared with placebo, sorafenib significantly extended both median overall survival (OS) and median progression-free survival (PFS) in patients with advanced HCC. This study established sorafenib as the standard first-line treatment for HCC.

Lenvatinib is a multi-target tyrosine kinase inhibitor that effectively blocks tumor growth and angiogenesis signaling pathways by inhibiting VEGFR, fibroblast growth factor receptors, and other kinases. It has become an important alternative to sorafenib in the first-line treatment of advanced hepatocellular carcinoma. Its key evidence comes from the international multicenter Phase III non-inferiority REFLECT trial [9], which demonstrated that lenvatinib was non-inferior to sorafenib in terms of overall survival in patients with previously untreated unresectable HCC, and showed superior performance in secondary endpoints such as progression-free survival and objective response rate. However, the study results primarily applied to patients with Child-Pugh class A liver function and did not cover high-risk subgroups such as those with portal vein invasion or extremely high tumor burden. Although lenvatinib has established its position in first-line treatment of advanced HCC, its drug resistance remains a concern that warrants continued attention. In addition, the LAUNCH study suggested [10] that lenvatinib combined with transarterial chemoembolization may provide further survival benefits compared with lenvatinib monotherapy.

2.3 New Standards in Targeted Therapy Combined with Immunotherapy

A key breakthrough in the treatment landscape came from the IMbrave150 study of atezolizumab combined with bevacizumab [9]. This global multicenter Phase III clinical trial was the first to demonstrate the superiority of a targeted-immunotherapy combination over sorafenib in the first-line treatment of unresectable hepatocellular carcinoma. Atezolizumab plus bevacizumab (the IMbrave150 regimen) achieved clinically meaningful and statistically significant improvements in both overall survival and progression-free survival, along with a significantly increased objective response rate and manageable safety profile. This regimen rapidly became the new standard of care for first-line treatment of advanced HCC, ushering in a new era in which targeted-immunotherapy combinations serve as the mainstream treatment modality [11].

Another important regimen emerged from the HIMALAYA study, which explored a different strategy from anti-angiogenic therapy combined with PD-L1 inhibition—namely, dual immune checkpoint inhibitor combination. This study evaluated the efficacy of durvalumab plus tremelimumab (dual immunotherapy) versus sorafenib as first-line treatment for unresectable liver cancer. The results showed that the dual immunotherapy regimen also provided a statistically significant overall survival benefit and exhibited a durable long-survival tail effect, offering patients an effective first-line option without the need for anti-angiogenic agents [12].

3. Comparative Analysis of Various Therapeutic Agents

Prior to the era of immune combination therapy, systemic treatment of advanced hepatocellular carcinoma (HCC) primarily relied on traditional cytotoxic chemotherapeutic agents. However, due to inherent limitations such as generally low objective response rates (typically below 20%) and significant toxicity, these drugs failed to substantially improve patient prognosis. Their limitations stem mainly from two aspects: first, most treated patients were in the advanced stage with high tumor burden and relatively inactive cancer cell proliferation, rendering them insensitive to chemotherapy; second, HCC cells often highly express multidrug resistance genes, leading to intrinsic resistance. Although newer agents such as gemcitabine were later explored, overall efficacy remained limited. Traditional systemic chemotherapy is still not recommended as a standard approach to improve patient survival.

Immune combination therapies represented by atezolizumab plus bevacizumab (IMbrave150 regimen) and durvalumab plus tremelimumab (HIMALAYA regimen) have become the first-line standard of care for

advanced HCC, both receiving the highest-level Category 1, Grade A evidence recommendation in major guidelines. The IMbrave150 regimen achieved a median overall survival of 19.2 months, significantly superior to sorafenib's 13.4 months, with an objective response rate of 30%. The HIMALAYA regimen yielded a median overall survival of 16.4 months, also superior to sorafenib's 13.8 months. In comparison, sorafenib, as the historical standard first-line therapy, retains a Category 1, Grade A recommendation in guidelines but is now primarily used in patients with contraindications to immune checkpoint inhibitors. For patients unsuitable for immunotherapy, the targeted agent lenvatinib has demonstrated non-inferior survival benefits compared with sorafenib and superior objective response rates. In the second-line setting, the approval of agents such as regorafenib, cabozantinib, and ramucirumab for patients with specific biomarkers provides clear and effective subsequent treatment options after failure of first-line therapy.

In terms of safety, bevacizumab in the IMbrave150 regimen significantly increases the risk of bleeding, particularly in patients with portal hypertension and esophageal or gastric varices; therefore, strict endoscopic screening and pretreatment are required before treatment. Although the HIMALAYA regimen avoids mandatory endoscopic screening, its dual immunotherapy approach is associated with a higher incidence of immune-related adverse events. Targeted agents such as sorafenib and lenvatinib have their own characteristic adverse event profiles.

Regarding applicability in specific populations, the IMbrave150 regimen requires attention to bleeding risk, and guidelines strongly recommend endoscopic screening before treatment for patients at risk of portal hypertension and varices. The HIMALAYA regimen does not require mandatory baseline endoscopy. In second-line treatment, ramucirumab is indicated only for patients with elevated alpha-fetoprotein levels.

For intermediate-stage HCC, strategies combining local therapies (such as TACE) with novel systemic treatments have shown initial promise. However, their long-term survival benefits have not been fully established, and combination therapy significantly increases treatment-related toxicity, requiring careful weighing in clinical decision-making. For early- and intermediate-stage HCC, the treatment system is already well established. Early-stage patients can achieve radical cure through surgical resection, thermal ablation, or other local modalities; liver transplantation is a curative option for eligible patients. For intermediate-stage patients, mature local control methods such as transarterial chemoembolization and selective internal radiation therapy serve as core treatments.

4. Future Directions

In recent years, the comprehensive treatment of advanced HCC has entered a new stage centered on targeted therapy combined with immunotherapy. Regimens represented by multi-target tyrosine kinase inhibitors plus immune checkpoint inhibitors have significantly improved objective response rates and overall survival in the first-line setting, driving the treatment landscape from targeted monotherapy toward immune-based combinations. Nevertheless, major challenges persist, including prominent primary and acquired drug resistance, and substantial differences in efficacy due to varying etiologies and tumor heterogeneity. To overcome these bottlenecks, future efforts should focus on in-depth exploration of resistance mechanisms such as immune microenvironment evolution and angiogenesis regulation, optimization of combination and sequential treatment strategies, and advancement of early clinical studies of antibody-drug conjugates (ADCs) combined with immunotherapy to strengthen the synergistic effects of tumor-targeted killing and immune modulation. At the same time, dynamic monitoring and efficacy prediction should be achieved through biomarkers and liquid biopsy technologies to identify the populations that benefit most from targeted-immunotherapy combinations. Molecular subtyping, individualized clinical trials, and whole-course management should be gradually integrated to collectively advance HCC treatment toward a more precise and systematic direction.

5. Conclusion

Prior to the targeted therapy era, liver cancer treatment mainly depended on traditional chemotherapeutic agents. However, due to low objective response rates and significant toxicity, their efficacy remained limited. The advent of sorafenib ushered in the targeted therapy era. Although it prolonged survival, monotherapy still faced bottlenecks. These limitations collectively drove the formation of the new paradigm of

combination therapy [16]. The IMbrave150 and HIMALAYA studies have jointly established the central role of targeted therapy plus immunotherapy in the first-line treatment of advanced HCC. These two studies not only confirmed the superiority of combination strategies but also enriched clinical treatment options. For specific patient populations, such as those intolerant to vascular endothelial growth factor inhibitors or with relevant contraindications, dual immunotherapy provides an important alternative. Subsequently, various targeted-immunotherapy combination regimens, such as sintilimab plus bevacizumab biosimilar and camrelizumab plus apatinib, have also achieved success, further consolidating this treatment model. These advances clearly demonstrate that systemic therapy for liver cancer has progressed from single-agent chemotherapy to single-agent targeted therapy, and now to the powerful combination of targeted therapy and immunotherapy. It has entered a brand-new stage characterized by synergistic enhancement, increasingly diversified treatment options, and a commitment to prolonging survival and improving quality of life.

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