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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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LETTER TO THE EDITOR

From biomarker discovery to combined therapies: Advancing hepatocellular carcinoma treatment strategies

Mo-Wei Kong, Yang Yu, Ying Wan, Yu Gao, Chun-Xiang Zhang

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Abstract

This editorial reviews advances in hepatocellular carcinoma (HCC) treatment, focusing on a triple therapy approach and biomarker discovery. Zhang *et al* discuss the synergistic potential of transarterial chemoembolization combined with tyrosine kinase inhibitors and PD-1 inhibitors. Meanwhile, Li *et al* identify protein tyrosine phosphatase non-receptor II (PTPN2) as a biomarker for poor prognosis and immune evasion in HCC. The studies highlight the importance of combined therapies and biomarkers in improving HCC treatment efficacy and patient outcomes, with PTPN2 emerging as a potential therapeutic target. This article supplements the aforementioned studies with more recent research advancements, focusing on the molecular mechanisms and clinical applications of biomarkers.

Key Words: Hepatocellular carcinoma; Triple therapy; Transarterial chemoembolization; Protein tyrosine phosphatase non-receptor II

Core Tip: This article reviews the integration of novel combined therapies and biomarker identification in hepatocellular carcinoma (HCC) management. The studies by Zhang *et al* and Li *et al* explore the efficaciousness of a triple therapy involving transarterial chemoembolization, tyrosine kinase inhibitors, and PD-1 inhibitors, and the prognostic value of protein tyrosine phosphatase non-receptor II (PTPN2), respectively. These investigations underscore the significance of PTPN2 as a potential therapeutic target and highlight the promise of synergistic treatment strategies in enhancing HCC patient outcomes.

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TO THE EDITOR

Hepatocellular carcinoma (HCC) is a significant contributor to cancer-related mortality worldwide. As our understanding of its molecular underpinnings grows, so too does the development of targeted and personalized treatment strategies. This editorial delves into recent breakthroughs in HCC therapy, highlighting the role of biomarkers and the emerging concept of triplet therapy.

The study by Zhang *et al*[1] explored the synergistic potential of transarterial chemoembolization (TACE) combined with tyrosine kinase inhibitors and PD-1 inhibitors. This integrated therapy not only targets tumor angiogenesis but also enhances the body's antitumor immune response through checkpoint inhibitors, offering new hope for HCC treatment. Simultaneously, Li *et al*[2] identified non-receptor type II protein tyrosine phosphatase (PTPN2) as a biomarker of poor prognosis and immune escape in HCC. The discovery of PTPN2 not only provides a new prognostic indicator for HCC but also suggests potential therapeutic targets. These studies underscore the significance of integrated therapies and biomarkers in enhancing treatment efficacy and prognosis in HCC patients.

Unveiling the molecular basis

The genomic landscape of HCC: HCC is a complex disease characterized by a diverse array of genetic and epigenetic alterations[3]. The genomic profile of HCC features a variety of mutations, copy number variations, and changes in gene expression, driving tumor initiation, progression, and metastasis. In HCC, cell cycle regulators and apoptosis-related gene families, such as CCND1 and CDK4, are key molecular players[4]. Their overexpression, as shown by Lee *et al*[5], is typically associated with poor prognosis and aggressive phenotypes in HCC. Moreover, the dysregulation of growth factors and their receptors, such as the VEGF family, crucial for angiogenesis, is a necessary condition for tumor growth and invasion[6]. The intricate interplay among these molecular components forms the foundation of HCC heterogeneity, requiring deeper understanding for the development of targeted therapies.

The role of lymph node metastasis-related genes: The propensity of HCC for lymph node metastasis is a major contributor to its poor prognosis[7]. As revealed by the genome-wide analysis by Lee *et al*[5] published in the *World Journal of Gastroenterology*, the upregulation and downregulation of genes related to HCC lymph node metastasis provide new insights into the molecular mechanisms of tumor metastasis. These genes, including *MET*, *EPHA2*, and *MMP2*, are involved in processes such as cell adhesion, migration, and extracellular matrix degradation[3,8]. The identification of these genes not only sheds light on the molecular mechanisms of tumor cell metastasis but also presents potential therapeutic targets. For instance, inhibiting matrix metalloproteinases (MMPs) like MMP2 and MMP13 may help limit the invasive capabilities of HCC cells, restricting metastasis and improving patient outcomes[9].

Integration of biomarkers and triplet therapy: The discovery of biomarkers in HCC has paved the way for personalized medicine, with therapies tailored to individual molecular characteristics. The integration of biomarkers with triplet therapy is an emerging frontier in HCC treatment. For instance, the discovery of immunotherapy biomarkers has transformed the systemic treatment of advanced HCC, exemplified by the success of the atezolizumab and bevacizumab combination[10]. Moreover, the combination of regional therapy, such as TACE, with immunotherapy is under active investigation. TACE, by increasing the release of tumor antigens, may enhance the efficacy of immunotherapy[11]. Ongoing phase 3 clinical trials, such as IMbrave150 and EMERALD-1, will provide critical evidence for this combined treatment approach[12].

Clinical translation of biomarker research

The clinical translation of biomarkers is a critical component of precision medicine, especially for HCC, a highly heterogeneous malignancy. Biomarkers in HCC not only reveal the molecular features of tumors but also predict patient responses to specific treatments, providing essential insights for clinical decision-making. In the latest IMbrave150 clinical trial, ISS and ISS10 were demonstrated to be promising predictive biomarkers that can enhance treatment outcomes for HCC patients receiving combination immunotherapy. These markers are crucial for optimizing patient stratification and personalized treatment approaches to improve the efficacy of standard care regimens[13]. The identification of

biomarkers is typically based on comprehensive analysis of the tumor genome, transcriptome, proteome, and metabolome[14]. For example, through high-throughput microarray technology, previous studies conducted gene expression analysis on tumor and non-tumor tissues from 32 HCC patients, uncovering gene expression patterns associated with lymph node metastasis[15]. These genes include cell membrane receptors, intracellular signaling, and cell adhesion-related genes, such as *MET*, *EPHA2*, *CCND1*, *MMP2*, and *MMP13*. Abnormal expression of these genes may promote tumor cell invasion and metastasis, offering new molecular targets for HCC treatment. Recent study have identified minichromosome maintenance 4, as a member of the minichromosome maintenance protein family, as a potential biomarker in pan-cancer analyses[16].

Despite the promise of biomarker discovery, their clinical application faces significant challenges. Firstly, biomarker validation requires testing in larger patient populations to ensure their generalizability and reproducibility. Additionally, biomarker detection methods need to be highly sensitive, specific, and user-friendly to meet clinical testing demands. For instance, previous studies confirmed microarray analysis results using real-time quantitative reverse transcription-polymerase chain reaction, a method that is accurate but may be complex and costly for clinical application[17]. Therefore, the development of simpler, more cost-effective detection methods is crucial for the clinical application of biomarkers.

Moreover, the clinical application of biomarkers must consider individual patient variations, such as genetic background, tumor subtype, and environmental factors[18]. These factors may influence biomarker expression and function, affecting their predictive value in clinical settings. Future research should further explore the relationship between these factors and biomarkers to improve the clinical effectiveness of biomarker applications. With the advancement of precision medicine, the study of personalized biomarkers will become a focal point. Personalized biomarkers can provide more accurate treatment predictions and guidance based on specific patient conditions, such as genetic background, tumor characteristics, and environmental factors. Individualized treatment strategies based on specific gene mutations or expression profiles may significantly enhance treatment outcomes while reducing adverse reactions.

CONCLUSION

This editorial discusses the pivotal role of biomarkers in HCC treatment and their transformative impact on precision medicine. Despite the potential of biomarkers identified in preliminary studies, their clinical application requires rigorous validation through large-scale, multicenter clinical trials to ensure their reliability and generalizability. The transition of biomarkers from research to clinical practice presents challenges, including the optimization of detection methods, consideration of individual differences, assessment of therapeutic efficacy and safety, and compliance with regulatory standards. The future of personalized treatment is promising, with biomarkers guiding precise therapeutic directions based on patient-specific conditions. Technological innovations, like artificial intelligence, big data analysis, and novel detection technologies, expedite the discovery, validation, and clinical application of biomarkers, enhancing detection accuracy and efficiency. However, it is important to emphasize that the reproducibility and variability of biomarker efficacy across different patient populations still pose challenges, necessitating further research for support.

FOOTNOTES

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