HHS Public Access

Author manuscript

Liver Res. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Liver Res. 2020 December ; 4(4): 159–160. doi:10.1016/j.livres.2020.11.006.

Hepatocellular carcinoma diagnosis and treatment: An overview⋆

Steven D. Colquhoun,

Department of Surgery, University of California Davis, Sacramento, CA, USA

Yu-Jui Yvonne Wan*

Department of Pathology and Laboratory Medicine, University of California Davis, Sacramento, CA, USA

For decades, chronic liver disease has remained an increasing global health threat. Despite vaccines and antiviral therapies, both hepatitis B and C remain enormous clinical problems. Hepatic steatosis has become a rapidly increasing worldwide concern that can be appropriately characterized as an evolving epidemic.[1] Around the world alcohol consumption is on the rise, while autoimmune conditions and environmental toxins all continue contributing to this seemingly universal health dilemma. The common denominator of chronic liver disease is progressive hepatic inflammation leading to fibrosis and cirrhosis. Although increased awareness and improved diagnostics may be beneficial in the management of liver disease overall, it remains ironic that without specific directed investigations, these conditions can smolder silently and progress undetected for years. The prime example and likely the most devastating consequence of unchecked chronic liver disease is the development of hepatocellular carcinoma (HCC). As chronic liver disease has increased, so too has the incidence of HCC, which has now become one of the most common global causes of cancer-related deaths.[1]

The options available for treating patients with HCC have been exceptionally limited. In 2007, after years of effort, a protein kinase inhibitor sorafenib was shown to be effective in the treatment of unresectable HCC.[2] This was the first systemic drug therapy approved for the treatment of primary liver cancer and the only drug, at that point, with the efficacy to significantly improve overall survival for patients with HCC. For the first time, this removed HCC from the shadows of an orphan disease and into the light of hope for HCC patients. Unfortunately, this drug falls short of a truly effective therapy, offering survival benefits measured only in weeks while adding exceptionally high costs. Nevertheless, this earlier success no doubt inspired new investment and renewed enthusiasm for researchers to find the answers necessary to conquer this otherwise demoralizing disease. Enormous efforts

*Corresponding author. Department of Pathology and Laboratory Medicine, University of California Davis Health, Sacramento, CA, USA, yjywan@ucdavis.edu (Y.-J.Y. Wan).

Authors' contributions

S.D. Colquhoun and Y.-J. Y. Wan wrote the manuscript.

⋆Edited by Peiling Zhu and Genshu Wang.

Declaration of competing interest

The authors declare that they have no conflict of interest.

have since been expended to further identify both the cellular and molecular mechanisms of HCC carcinogenesis. Despite this, the development of a new HCC treatment has been slow. Eleven years after the FDA approval of sorafenib, another multiple receptor tyrosine kinase inhibitor, lenvatinib, was approved. While it has shown improved progression-free survival in patients with HCC, clearly better, more effective drugs are desperately needed. An effective cancer treatment strategy should target the pathways by which cancer arises in the first place. Thus, the identification of novel biomarkers will lead to earlier, more accurate, less invasive, and widely available diagnostic techniques. Early identification itself will lead to improved clinical outcomes using existing treatment options. Even more exciting will be new drugs, treatment techniques, and strategies that will alter the assiduous progression of HCC as a leading cause of death. Finally, a better understanding of the mechanisms of chronic liver disease and HCC will lead to improved approaches to the goal of disease prevention. This single topic issue is divided into first several review articles, followed by those with original data.

For many years the only clinically relevant diagnostic biomarker for use in individuals suspected or known to be harboring HCC has been serum alpha-fetoprotein (AFP). Normally produced only in fetal livers, AFP is found to be elevated in approximately 70% of patients with HCC. This also means that almost 1/3rd of HCC patients do not have an elevated AFP and may miss the diagnosis using this biomarker. It is further true that AFP can be non-specifically elevated even in the absence of malignancy. Clearly alternative biomarkers with greater sensitivity and specificity would be helpful in the management of this disease. One such candidate is a membrane-associated glycoprotein, Golgi Protein 73 (GP73). A better understanding of this oncogene may provide for greater accuracy in diagnosis and monitoring of treatment, in addition, it may also represent a future target for new therapies. In this issue, Drs. Wang and Wan[3] provide a comprehensive review of the most recent data regarding GP73 and bring us up to date on this promising biomarker. Another biomarker with potential significant relevance to the diagnosis and treatment of HCC is glypican-3 (GPC3). This protein has been found to have a specific expression on certain HCC tumors. In this issue, Shih *et al.*[4] provide a compendium of relevant details regarding GPC3, including its structure, tissue distribution, apparent biological functions and what is known regarding its potential as a new diagnostic and/or prognostic biomarker as well as target for new directed therapies. Moreover, in recent years, certain members of the Galectin (Gal) family have been found to be overexpressed in HCC. In this issue, Setayesh *et al.*[5] provide an exhaustive analysis of Gals in general, and Gal-1 and −3 as they pertain to mechanisms of HCC development. These proteins appear to have multiple roles in liver carcinogenesis as well as clinical relevance in survival. Those Gal family members will likely play a part not only in diagnosis and prognosis but also as a novel target for new therapeutics.

As research into HCC progresses at multiple levels and on many fronts outside the clinical realm, it is important to maintain a perspective of what treatment modalities are currently in clinical practice and how they are utilized based on the various presentations of patients with HCC.[6] The clinical practice of managing this disease is in constant evolution and it should be of importance to researchers working at all levels to keep pace with the seeming multitude of treatment options available. This special issue includes an update from the

clinical front line in the battle against HCC. This disease often does not lend itself to definitive prospective, randomized, placebo-controlled clinical trials. It can be frustrating to realize how much “art” is at play in the management of HCC patients. To a non-clinician, it can appear that various treatment modalities and interventions are often employed randomly. In reality, a patient is treated is a function of many factors including the tumor, the patient, the physicians, and the institution. This clinical perspective will hopefully provide some insight into this otherwise confusing arena. The final review is exceptionally important as it delves into the burgeoning field of immunotherapy, epigenetics, and the increasingly relevant role of the gut microbiome. Reading this review by Vaziri *et al.*,[7] one might be struck by a thrilling glimpse into the future of understanding and influencing the development and treatment of HCC. This review also nicely integrates what we have learned in the above three reviews, placing them all in the framework of what may soon be possible. Modulating the tumor microenvironment will certainly play an increasing role with this disease.

The second half of this issue includes exciting new clinical data on both the diagnosis and treatment of HCC. As noted above, the tyrosine kinase inhibitor lenvatinib is a relatively new agent in the HCC armamentarium. Dr. Ohki and colleagues[8] present clinical data regarding some important, almost nuanced, dosing details that appear to make the difference in achieving a meaningful patient outcome with this new drug. Such data offers critical incremental steps forward in optimal clinical management. One longstanding treatment option available for many patients with HCC is thermal ablation of candidate lesions. Having an effective treatment *per se* is only a first step as it is equally important to define the circumstances for its use. When and how to use a therapy makes the difference between helping or harming a patient, and one increasingly relevant factor is a patient’s age. In this issue, Dr. Ohki and his team present interesting data that further extends our understanding of when thermal ablation can be safely employed.[9] Finally, in this special issue, we find new data regarding the transcriptional co-factor protein Yes-associated protein-1 (YAP-1). YAP-1 is likely an oncogene that becomes altered during liver carcinogenesis. Dr. Zhang and collaborators present clinical data, which provides some intriguing insights into the potential of YAP-1 as a future diagnostic and prognostic biomarker as well as a potential target for therapy.[10]

In this dedicated single topic issue of *Liver Research*, the reviews and original data presented show striking examples of the breadth and sophistication of current ongoing research in this growing health crisis. From this collection of works, we gain a better understanding of the mechanistic, diagnostic, and therapeutic fronts in which great progress is occurring in the battle against this dreadful disease.

Acknowledgements

This manuscript is supported by grants funded by the USA National Institutes of Health U01CA179582 and R01CA222490.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBO-CAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. [PubMed: 30207593]
2. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390. [PubMed: 18650514]
3. Wang Y, Wan YJY. Golgi protein 73, hepatocellular carcinoma and other types of cancers. Liver Res 2020;4:161–167. [PubMed: 33343966]
4. Shih TC, Wang L, Wang HC, Wan YJY. Glypican-3: a molecular marker for the detection and treatment of hepatocellular carcinoma. Liver Res 2020;4: 168–172.
5. Setayesh T, Colquhoun SD, Wan YJY. Overexpression of Galectin-1 and Galectin-3 in hepatocellular carcinoma. Liver Res 2020;4:173–179.
6. Colquhoun SD. Hepatocellular carcinoma clinical update: current standards and therapeutic strategies. Liver Res 2020;4:180–190.
7. Vaziri F, Colquhoun SD, Wan YJY. Hepatocellular carcinoma immunotherapy: the impact of epigenetic drugs and the gut microbiome. Liver Res 2020;4: 191–198. [PubMed: 33343967]
8. Ohki T, Sato K, Kondo M, et al. Relationship between outcomes and relative dose intensity of lenvatinib treatment in patients with advanced hepatocellular carcinoma. Liver Res 2020;4:199–205.
9. Tsuchiya K, Ohki T, Sato K, Kondo M, Toda N, Tagawa K. Efficacy of percutaneous radiofrequency ablation for hepatocellular carcinoma treatment in patients aged ≥80 years. Liver Res 2020;4:206–211.
10. Qian X, Zhang W, Shams A, et al. Yes-associated protein-1 may serve as a diagnostic marker and therapeutic target for residual/recurrent hepatocellular carcinoma post-transarterial chemoembolization. Liver Res 2020;4:212–217.