Editorial

JOURNAL OF HEPATOLOGY

Milestones in the pathogenesis and management of primary liver cancer

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Summary

Liver cancer is a major global health problem whose incidence is on the rise. The improvement in the understanding of the pathogenesis, early detection, diagnosis, staging and treatment of liver cancer has been enormous. The landscape of molecular aberrations driving both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) have been unravelled. Several breakthroughs have occurred in the prevention, surveillance and treatment of HCC. Particularly, management of patients at advanced stages has changed dramatically during the last decade with the advent of effective systemic therapies such as sorafenib, lenvatinib, regorafenib, cabozantinib and ramucirumab. iCCA has long been considered a difficult to treat disease with few therapeutic options. However, recent advances in our understanding of its molecular pathogenesis, as well as the development of adjuvant therapy (capecitabine) and new systemic treatments (gemcitabine and cisplatin) have paved the way for further innovations in the management of patients with iCCA. In this manuscript, we aimed to highlight the main milestones in the medical history of primary liver cancer and report the most recent developments described within this special issue.

Introduction

The field of primary liver cancer has moved quickly. What was once an orphan disease, usually diagnosed at advanced stages with no curative or palliative treatment options, is now an area of huge research interest – there have been major breakthroughs in the understanding of its pathogenesis, as well as in the development of diagnostic tools and therapeutic options. Nevertheless, the clinical management of HCC and iCCA remains complex and requires a multidisciplinary management team including hepatologists, oncologists, liver surgeons, radiologists and pathologists.

The improvement in the understanding of the pathogenesis, early detection, diagnosis, staging and treatment of liver cancer has been enormous.[1] Just in the case of HCC, it would be difficult to select the most relevant advances, which sometimes correlate with the most impactful manuscripts and breakthroughs in management (Fig. 1). First, the direct association between HBV/HCV infection and HCC development was identified.[2,3] In terms of prevention and surveillance, universal vaccination for HBV and surveillance with ultrasound (with/without alpha-fetoprotein measurements) have been established as providing clinical benefit in patients at risk.[4–7] Non-invasive imaging-based criteria for HCC were already established in 2001.[8] In terms of understanding the pathogenesis of the disease, major improvements have occurred since the initial discovery of p53 mutations, with the recent establishment of a mutational landscape and detailed molecular classifications.[9,10] Regarding staging systems, Okuda staging[11] was replaced in 1999 by the BCLC staging system, mostly used in the Western world, and the Hong-Kong staging system, used in more recent years in Asia.[12,13] In terms of management, major advances in defining candidates for resection,[14] transplantation[15,16] and local ablation[17] occurred between 1996–2001, with chemoembolisation established as standard of care by 2002-03.[18,19] Since then, there have been no major improvements in outcomes for these patients, despite the refinements in techniques and novel devices.[20,21] Assessment of response to locoregional therapies was first defined by EASL criteria and more recently with RECIST/modified RECIST (mRECIST) criteria.[22,23] Major milestones have occurred in the management of advanced cases, from sorafenib becoming the first systemic molecular therapy effective in HCC,[24] to the demonstration of clinical benefit with several tyrosine kinase inhibitors (lenvatinib, regorafenib, cabozantinib and ramucirumab)[25–28] and the identification of immune checkpoint molecules as relevant therapeutic targets (alone or in combination regimens).[29,30] Even combination strategies (*i.e.* atezolizumab plus bevacizumab) are emerging as the new gold standard for the coming years. All these drugs have complicated the sequence of treatments and the management of adverse events in these patients.

Received 11 November 2019; accepted 13 November 2019

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https://doi.org/10.1016/j.jhep.2019.11.006

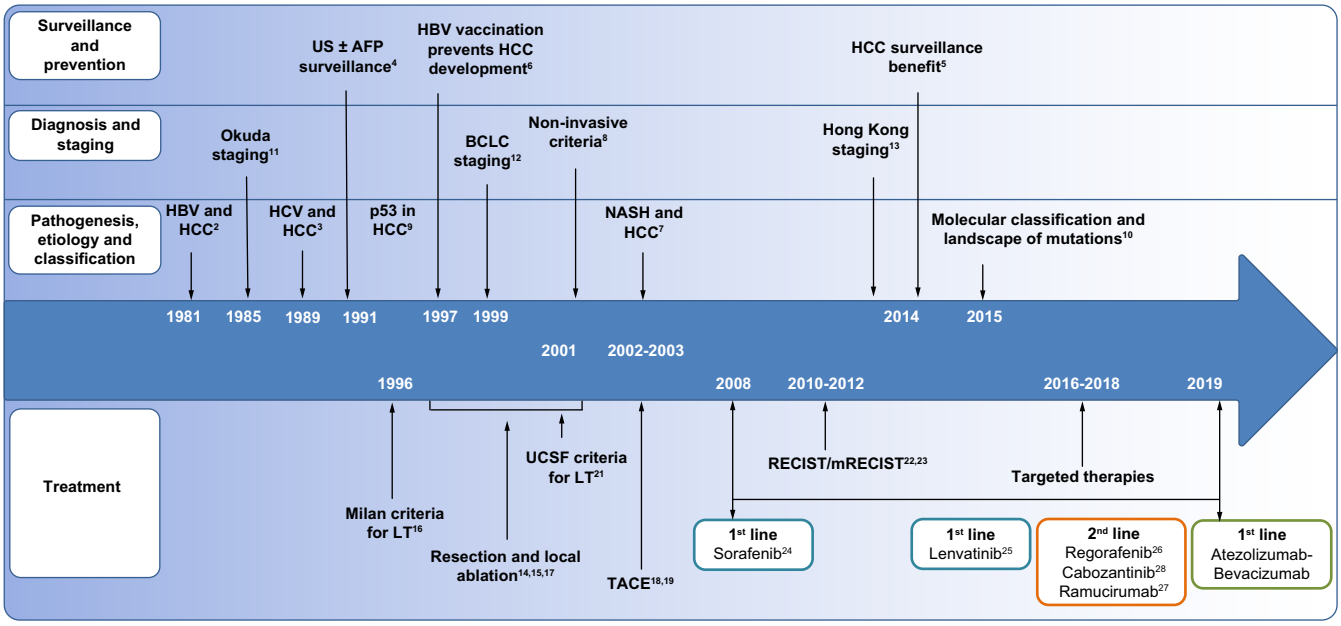

Fig. 1. Milestones in the pathogenesis and management of hepatocellular carcinoma. Summary of major advances in pathogenesis, surveillance and prevention, diagnosis and staging as well as treatment of hepatocellular carcinoma from 1980-2020. This figure aims to capture major milestones, although there are other important advances that have not been incorporated due to space constraints.

In parallel, major advances have occurred in our understanding of the pathogenesis, diagnosis and management of iCCA. Recently, the first guidelines on the management of iCCA were reported.[31] Refinements have been proposed for the selection of candidates for resection and even transplantation at very early stages.[32] Systemic chemotherapies in the first-line (gemcitabine and cisplatin)[33] and in the adjuvant setting (capecitabine)[34] have been established as standard of practice. Finally, as a result of the discoveries of major molecular drivers (*i.e. FGFR2* fusions, *IDH1* mutations),[35] several drugs tested in phase II trials with positive signals of efficacy are currently being tested in biomarker-enriched phase III trials.

This special edition of *Journal of Hepatology* provides cutting-edge information on the main topics related to the pathogenesis and management of liver cancer. In this article we aim to highlight the major milestones in the medical history of primary liver cancer and pinpoint the main novel advances described in the manuscripts of this special issue. We hope that those 12 articles might be useful to health professionals and scientists involved in the research and care of patients suffering from these dreadful diseases.

Pathogenesis of hepatocellular carcinoma

In the eighties and the nineties, major advances increased our understanding of the pathogenesis of HCC: a) identification of key genetic drivers in liver carcinogenesis (identification of *TP53* mutations and the relationship with Aflatoxin B1 exposition, identification of activating mutations of B-catenin as a key oncogene), b) dissection of the mechanisms of hepatitis B carcinogenesis such as insertional mutagenesis and c) the development of genetically engineered mouse models of HCC development.[9,36–40] However, the methods used to decipher tumour genomics or to develop cellular or mouse preclinical models were expensive, time consuming and only mimic a part of the human disease.

Recent technological breakthroughs such as next generation sequencing have enabled the sequencing of a whole tumour exome, genome or transcriptome in a few hours. Sequencing data from whole exome and whole genome sequencing have highlighted the main signalling pathways altered in HCC (telomere, cell cycle, Wnt/β-catenin, epigenetic, NRF2/KEAP1, RAS/RAF/MAPK and AKT/mTOR pathways).[41–44] These new data have helped us to understand the link between genetic alterations and transcriptomic alterations, as well as clinical and pathological features defining homogenous subgroups of HCC.[45–47] Several integrative molecular classifications have been published as well as prognostic molecular signatures derived from the tumour and non-tumour liver.[48–50] In this special issue of *Journal of Hepatology*, Rebouissou *et al.* describe the main genetic and transcriptomic data on HCC and the potential translation of genomic knowledge into clinical practice.[51]

Moreover, the microbiota plays a role in various human diseases such as obesity, diabetes, infectious diseases and autoimmune disease. The role of microbiota in cancer development, its relationship with antitumour immune responses and responses to systemic treatment, including cytotoxic chemotherapy and immunotherapy, have recently been described in cancer, including HCC.[52–54] Schwabe *et al.* highlight the role of microbiota in HCC development and as a potential therapeutic target.[55] Finally, preclinical models are a useful tool to understand the pathogenesis of liver carcinogenesis and test new drugs targeting the immune system or signalling pathways.[56–59] The recent advances in generating new preclinical models of HCC (cell lines, organoids, mouse models, patient-derived xenografts) that could recapitulate human HCC and identify new drugs that are potentially useful to treat primary liver cancers are summarised by Bresnahan *et al.*[60]

New trends in epidemiology and surveillance of HCC

Over the last decades we have witnessed some important transformations in the epidemiology of HCC. HBV vaccination programmes have been widely implemented in countries around the globe, and eradication of HCV through the use of direct-acting antivirals is a target in many others.[61,62] While virally induced tumours will soon become less frequent, alcohol-related cirrhosis is a stably prevalent pre-neoplastic condition, and chronic fatty liver disease associated with metabolic syndrome is a growing cause of HCC even in the absence of cirrhosis.[63]

All these changes will have an impact on surveillance policies that Singal *et al.* review nicely in this special issue.[64] While the need for surveillance is clear in a disease with frighteningly similar incidence and mortality rates, only a minority of patients at risk get screened. Some conundrums around screening policies seem difficult to untangle. Information is the key to adherence. Some important efforts have been made to improve risk stratification and individualise screening in hepatitis B, and other aetiologies should follow this path. Discovery and validation of optimal serum biomarkers will certainly help to tip the scale of cost-effectiveness.

Resection and transplantation of hepatocellular carcinoma

Transplantation enables surgical removal of HCC tumours when the lack of sufficient liver functional reserve contraindicates partial resection in a cirrhotic liver. However, the times when cirrhosis was considered an almost absolute contraindication for liver resection are over, and Vibert *et al.* summarise the recent advances in surgical treatment of HCC.[65] Lower morbidity rates associated with the laparoscopic approaches, and personalised prognostication based on the volume and quality of the future liver remnant, the degree of portal hypertension, and the risk of tumour recurrence have changed the way surgery is considered in the treatment paradigm for HCC.[66,67] Along this line, the concept of transplant benefit is now at the heart of multidisciplinary team discussions even when living donation removes the barrier of organ availability.[68] In a shift of the pendulum, restrictions based on tumour burden are expanding and frequently take into consideration the biological behaviour of the disease during locoregional therapies in downstaging strategies.

Locoregional treatment of hepatocellular carcinoma

Another major change in the landscape of HCC management is the role of locoregional therapy, particularly transcatheter arterial chemoembolisation (TACE).[18] Palmer *et al.* summarise the major issues of TACE, including risk stratification for patient selection, transition from TACE to systemic therapy, and the use of TACE or other locoregional therapies (such as transcatheter arterial radioembolisation) for patients with earlier stage disease (for downstaging).[69] Data from clinical trials of combinations of TACE and systemic therapy for BCLC stage B or stage C patients, which are unfortunately all negative, were reviewed in detail.[70,71] Potential reasons behind the failure of these combination trials, as well as the prospects for future trial design, particularly for trials combining immune checkpoint inhibitors, were discussed in the reviews by Palmer *et al.* and Cheng *et al.*

Assessment of radiological response

mRECIST criteria were proposed as a way of adapting the RECIST criteria to the particularities of HCC.[23] This proposal intended to overcome some limitations of RECIST in measuring tumour shrinkage with local and systemic therapies, and also to refine the assessment of progression that could be misinterpreted with conventional RECIST 1.1, due to clinical events related to the natural progression of chronic liver disease (development of ascites, enlargement of lymph nodes, *etc.*). Since then, mRECIST has served its purpose since being adopted or included in clinical practice guidelines[1,22,72,73] for the management of HCC; it has also been instrumental for assessing response and time-to-event endpoints in several phase II and III investigations. Nowadays, mRECIST has become the standard tool for measurement of radiological endpoints at early/intermediate stages of HCC. At advanced stages, guidelines recommend both methods. mRECIST has been proven to capture higher objective response rates in tumours treated with molecular therapies and those responses have shown to be independently associated with better survival. In their contribution, Llovet and Lencioni[40] review the performance of mRECIST during the last decade, incorporating novel clarifications and refinements in light of changes in the treatment landscape at advanced stages of the disease. Similarly, they discuss progression-free survival as a primary endpoint in some phase III investigations, as effective therapies applied beyond progression might mask overall survival results.

Immunotherapy in the management of hepatocellular carcinoma

Immune checkpoint inhibitors were the first agents other than tyrosine kinase inhibitors to be approved for the treatment of HCC in several countries. This was largely based on the observation from single-arm phase II trials that some patients experienced very intense, even complete responses that were durable and also associated with extended survival.[29,30] However, their effect on the overall survival of patients in the advanced stage was not confirmed in the first available controlled trials in the first line *vs.* sorafenib, or in the second line *vs.* best supportive care. Recently, a combination of the anti-PD-L1 antibody atezolizumab and the antiangiogenic agent bevacizumab was the first treatment shown to improve on the benefit of sorafenib.[74] Hence, there is little doubt that immunotherapy will be in the toolbox of systemic therapies for HCC, alone or in combination. Although checkpoint inhibitors are by and large well tolerated, they can also result in significant and even life-threatening toxicities due to their ability to enhance T cell activation.[75] The management of such toxicities in patients with HCC, who usually suffer from advanced chronic liver disease, is different than for patients with other tumours and can be challenging. Sangro *et al.* review the available information, summarise the challenges that cirrhosis poses to diagnosis and management, and provide specific recommendations for liver toxicities.[76] This will be a useful aid for hepatologists, medical oncologists and any other specialist involved in the care of patients with HCC.

Tyrosine kinase inhibitors for advanced hepatocellular carcinoma

After nearly a decade of struggling with negative results from randomised trials of drug therapy for advanced HCC, new data

emerging over the past 3 years has transformed the landscape of clinical management for HCC and also ignited great enthusiasm in developing novel agents, as well as combination strategies.[24,26–28] Faivre *et al.* discuss the challenges of identifying targetable molecular aberrations and biomarkers for efficacy prediction in HCC, and provide a comprehensive overview of currently approved targeted therapies for advanced HCC, including sorafenib and lenvatinib in the first-line setting, and regorafenib, cabozantinib and ramucirumab in the second-line setting.[77] The authors encourage us to "think outside the box" by exploring novel therapeutic targets (*e.g.*, immune checkpoints, transforming growth factor-β, c-MET, and fibroblast growth factor) and adopting combination strategies.

Combinations of immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1) pathway and anti-angiogenic therapy have become the mainstream of combination therapy trials for HCC.[78,79] Faivre *et al.* summarise the scientific rationale behind this combination strategy and the promising data from early-phase trials of combination therapy for HCC,[77] while Cheng *et al.* further elaborate on recent advances in the development of predictive biomarkers, and explore the immune-related antitumour mechanisms of multikinase inhibitors (independent of their anti-VEGFR effects).[80] They also discuss the challenges of further development of different immunotherapy-based combination therapies, including selection and prioritisation of regimens based on limited preclinical and clinical data, and evaluation and management of adverse events.[80,81]

Curative treatments of intrahepatic cholangiocarcinoma

iCCA is a highly lethal hepatobiliary neoplasm whose incidence is increasing. This rare malignancy has recently received considerable clinical and investigative attention. Several advances have been made in the past decades to better understand this complex malignancy and to develop new treatment strategies, nonetheless the prognosis of iCCA remains dismal. Mazzaferro *et al.* provide an update on the advances in liver resection as the mainstay of treatment.[54] Nowadays, properly selected candidates achieve 5-year survival rates of 25%–40%.[82,83] Adjuvant chemotherapy is recommended in high-risk patients (multifocal disease, large lesions, positive lymph nodes or R1 resection) with capecitabine for 6 months.[34] Recent retrospective studies have shown that liver transplantation might be a treatment option for patients with unresectable very early iCCA (*i.e.* ≤2 cm), whereas a combination of neoadjuvant therapies and liver transplantation may also be an option for patients with locally advanced iCCA, but prospective studies with predetermined selection criteria are needed.

Systemic treatments of intrahepatic cholangiocarcinoma

iCCAs are sensitive to chemotherapy. Kelley *et al.* report the standard of practice in front-line advanced iCCA as being gemcitabine and cisplatin, following the seminal trial of 2010.[33] In their review, recently reported positive clinical trials are analysed, particularly capecitabine in the adjuvant setting.[34] Compared to HCC, iCCA is genetically distinct with several targetable genetic aberrations identified to date.[35] The most prevalent targetable mutations are *FGFR2* fusions and *IDH1* mutations. Nowadays, clinical data is emerging on targeting these oncogenic drivers pharmacologically. Positive phase II results have been reported with FGFR2 inhibitors,[84,85] and phase III data reported positive PFS with ivosidenib (IDH1 inhibitor).[86] Also, the role of immunotherapy has been examined and is an area of intense investigation. Kelley *et al.* review these advances and highlight future research directions.[87]

Financial support

Josep M. Llovet is supported by National Cancer Institute (P30-CA196521), U.S. Department of Defense (CA150272P3), European Commission/Horizon 2020 Program (HEPCAR, Ref. 667273-2), EIT Health (CRISH2, Ref. 18053), Accelerator Award (CRUCK, AECC, AIRC) (HUNTER, Ref. C9380/A26813), Samuel Waxman Cancer Research Foundation, Spanish National Health Institute (SAF2016-76390) and the Generalitat de Catalunya/AGAUR (SGR-1358).

Conflicts of interests

JC Nault declared no conflict of interests related with this topic. Ann-Lii Cheng has received consulting or lecture fees from Bayer HealthCare Pharmaceuticals Inc., Eisai, Bayer Yakuhin, Ltd., Merck Sharp & Dohme, Eisai, Merck Serono, Novartis, Ono Pharmaceutical, Exelixis, Nucleix Ltd., Roche/Genentech, Bristol-Myers Squibb, Shanghai Hengrui Pharmaceutical Co., Ltd., and IQVIA. Bruno Sangro has received consulting or lecture fees from Adaptimmune, Astra Zeneca, Bayer, BMS, BTG, H3 Biomedicine, Ipsen, Lilly, Merck, Onxeo, Roche/Genentech, Sirtex Medical, and Terumo; and research grants from BMS, Onxeo, and Sirtex Medical. Josep M Llovet is receiving research support from Bayer HealthCare Pharmaceuticals, Eisai Inc, Bristol-Myers Squibb and Ipsen, and consulting fees from Bayer HealthCare Pharmaceuticals, Eli Lilly, Bristol-Myers Squibb, Eisai Inc, Merck, Celsion Corporation, Exelixis, Ipsen, Glycotest, Navigant, Leerink Swann LLC, Midatech Ltd, Fortress Biotech, Sprink Pharmaceuticals, Nucleix and Can-Fite.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.11.006.

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Author names in bold designate shared co-first authorship

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