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Recent Developments and Therapeutic Strategies against Hepatocellular Carcinoma

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Introductory Statement

Hepatocellular carcinoma (HCC) has emerged as a major cause of cancer deaths globally. The landscape of systemic therapy has recently changed, with six additional systemic agents either approved or awaiting approval for advanced stage HCC. While these agents have the potential to improve outcomes, a survival increase of 2–5 months remains poor and falls short of what has been achieved in many other solid tumor types. The roles of genomics, underlying cirrhosis, and optimal use of treatment strategies that include radiation, liver transplantation, and surgery remain unanswered. Here, we discuss new treatment opportunities, controversies, and future directions in managing HCC.

Introduction

The death rate from hepatocellular carcinoma (HCC) is rising faster than that of any other cancer in the United States and it is predicted to be the fourth leading cause of cancer-related death in 2019 (1). While historic risk factors for liver cancer that include chronic hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol are addressed through a spectrum of prevention methods, new etiologic factors, obesity, type II diabetes, metabolic syndrome,

and nonalcoholic fatty liver disease (NAFLD), portend an increasing trajectory in the incidence of this disease (1). The estimated 5-year survival rate for HCC is 18%, which largely reflects that only 30%–40% of patients are diagnosed at an early stage and are eligible for curative-intent treatments such as surgical resection, ablation, or liver transplantation. Patients with curable HCC are almost always identified through screening programs, highlighting the importance of early detection. Both therapeutic and predisease interventions will need to be deployed now to blunt the impact of these risk factors in the decades to come.

Patients with HCC are not only afflicted with cancer but usually have underlying cirrhosis, thereby presenting major challenges across multiple disciplines. Despite some recent progress in the development of novel systemic therapies for HCC, long-term survivals for patients with advanced stage disease are very rare. The majority of patients are diagnosed with more widespread liver-confined disease [Barcelona Clinic Liver Classification (BCLC) stage B] or with vascular invasion or metastatic HCC (BCLC stage C). Integrated approaches utilizing animal models and The Cancer Genome Atlas (TCGA)–driven approaches to biomarker-driven clinical trials harnessing imaging, surgery/transplantation, radiation modalities, and chemo/immune therapeutics remain absent. To better understand the scope of HCC and to begin to advance therapy, leading investigators in the field convened at a workshop at the NCI in Bethesda, Maryland on November 11, 2018, in collaboration with the NCI HCC Working Group of the Radiation Research Program, American Association for Cancer Research (AACR), and American Association for the Study of Liver Diseases (AASLD). The following report highlights some of the conclusions, challenges, and controversies regarding novel therapies discussed at the workshop.

Novel Directions in HCC, Unanswered Questions, and Controversies

Surveillance is associated with improved survival in patients with cirrhosis (2). However, the effectiveness of HCC surveillance in clinical practice is limited by underuse and poor sensitivity of current tools for tumor detection. Novel biomarkers such as AFP-L3, DCP, osteopontin, glycosylated proteins, methylated DNA markers, and circulating tumor cells reveal promising results in phase II studies but require validation in phase III studies (2). To date, the development and validation of a new generation of biomarkers reflecting complex processes such as inflammation have not been deployed. Such biomarkers would be invaluable for prevention strategies as well (3). The most significant variants in HCC, confirmed through TCGA for HCC, included *TERT* promoter mutation (46%), *TP53* (31%), *CTNNB1* (27%), *ALB* (13%), *AXIN1* (8%), *RB1* (4%), and chromatin remodeling genes (ARID1A, 7%; *ARID2*, 5%; *BAP1*, 5%), and TGFβ pathway members (38%; refs. 4, 5). Animal models for prevention strategies are few, and validation in human studies is required for agents such as vitamin D, aspirin, and statins in younger high-risk patients. The urgent need for integrating biomarkers extracted from whole-genome characterization efforts on HCC, with animal models and validating these findings in large cohorts was highlighted (5–9). The paucity of biopsies & resected tissues for measuring biomarkers identified through TCGA was brought up as a major hurdle. The dearth of clinically validated commercially available biomarkers was also cited as the reason for HCC diagnosis and treatments lagging decades behind multiple other solid tumors.

Transarterial chemoembolization (TACE) has been the standard of care in intermediate-stage HCC (BCLC stage B) based on improvements in overall survival (OS) compared with supportive care alone in two randomized studies conducted prior to the approval of sorafenib. In patients with locally advanced HCC, randomized studies of transarterial radioembolization (TARE) versus sorafenib have shown improvements in progression-free survival (PFS), but not OS. A small randomized phase II trial in HCC with macroscopic vascular invasion demonstrated improved PFS and OS in patients treated with external beam radiotherapy (EBRT) and TACE compared with sorafenib, representing a new treatment paradigm (10).

Sorafenib, an oral TKI targeting VEGFR1–3, B-RAF, and PDGFRα, has been the first systemic therapy available for advanced HCC as a result of a phase III trial that demonstrated survival benefits versus placebo (median overall survival 10.7 months versus 7.9 months; HR 0.69; 95% confidence interval (CI), 0.55–0.87; $P < 0.001$; ref. 11). Adverse events are manageable, but associated to intolerance and treatment discontinuation in 10%–15% of patients. As a result, sorafenib has been the standard of care as the first-line option for advanced HCC accepted by guidelines for the last decade. Lenvatinib, an oral TKI targeting VEGFR 1–3, FGFR 1–4, RET, KIT, and PDGFRα, represents the recent success of targeted therapies for HCC. An international, multicenter, randomized, open-label, noninferiority phase III trial in HCC (REFLECT) demonstrated noninferiority with regard to OS of lenvatinib versus sorafenib and showed an improvement in secondary efficacy endpoints, including objective response (24% for lenvatinib vs. 9% for sorafenib as per modified RECIST criteria that address response evaluation including uptake in the arterial phase of contrast-enhanced imaging reflecting viable tumor–tumoral tissue) and PFS (7.3 months for lenvatinib vs. 3.6 months for sorafenib; refs. 12, 13). Of note, patients with ≥50% liver tumor involvement, clear invasion into the bile duct, or main portal vein invasion were excluded (12). On the basis of this noninferiority trial, lenvatinib was approved for the first-line treatment of patients with unresectable HCC.

Targeted therapies that demonstrated a survival benefit versus placebo in the second-line setting after prior sorafenib now include regorafenib, cabozantinib, and ramucirumab. Regorafenib is an oral multikinase inhibitor that inhibits VEGFR kinases with additional activity against angiopoietin 1 receptor (TIE2), KIT, and RET. Regorafenib is structurally similar to sorafenib, differing only by a single fluorine atom, but has greater potency against VEGFR *in vitro.* Regorafenib resulted in a significant improvement in OS (10.6 months vs. 7.8 months with placebo) in a randomized, placebo-controlled phase III trial (RESORCE) for patients with advanced HCC who tolerated sorafenib but experienced disease progression (2). Cabozantinib is a small-molecule multitarget TKI that inhibits VEGFR2 as well as Met and Axl. CELESTIAL was a randomized, placebo-controlled phase III trial of cabozantinib in patients who had HCC progression on prior sorafenib, as well as those intolerant to sorafenib due to its toxicities (that include dermatologic: hand–foot skin reactions, diarrhea, fatigue). The trial was stopped at an interim analysis that revealed an improvement in OS with cabozantinib (10.2 months vs. 8.0 months for placebo; ref. 14). Progression-free survival also favored cabozantinib (5.2 vs. 1.9 months with placebo). Ramucirumab is an antiangiogenic mAb that blocks downstream signaling by the VEGF2 receptor. Importantly,

ramucirumab is the first agent with clinical benefit in a biomarker-selected HCC patient population with baseline serum AFP ≥400 ng/mL (15).

ICIs targeting the programmed cell death protein 1 (PD-1) pathway have activity against diverse tumors and two PD-1 inhibitors, nivolumab, and pembrolizumab, were recently granted accelerated approval for HCC after treatment failure on sorafenib. Both agents demonstrated RECIST objective response rates of 15%–20% with monotherapy in HCC, with an impressive median duration of response of approximately 10 months in the phase II portion of the Checkmate-040 study (7). Confirmatory randomized phase III clinical studies of these agents in HCC are ongoing, including nivolumab versus sorafenib in the first-line setting (NCT02576509/CheckMate-459) and pembrolizumab versus best supportive care in the second-line setting (NCT02702401/KEYNOTE-240). Reportedly, KEYNOTE-240 failed to meet its coprimary endpoint of PFS and OS, although both end points significantly favored pembrolizumab; the trial is not formally reported yet. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors such as ipilimumab and tremelimumab have also shown clinical activity in HCC and are under investigation in combination with PD-1/PD-L1 blockade. Another ongoing global phase III study compares an alternative PD-L1 inhibitor, durvalumab and tremelimumab, versus durvalumab monotherapy and sorafenib monotherapy (NCT03298451/HIMALAYA). These studies will help to define where ICIs belong in the evolving treatment landscape of HCC.

While trials investigating the combination of sorafenib plus locoregional therapies (LRT) have failed to show clinical benefit compared with TACE alone (16), several preclinical studies have demonstrated potential synergy between various LRTs and ICIs. For example, immunogenic cell death induced by LRTs can induce the release of tumor-derived antigen and danger-associated molecular pattern signals that may synergize with immunotherapies to generate systemic antitumoral immunity that promotes abscopal regression of distant tumors. A number of clinical studies are now exploring various combinations of ICIs and LRTs for intermediate stage HCC (BCLC stage B). However, questions remain about the underlying biology of cell death from LRT, the differential effects of various modalities (TACE, TARE, EBRT, ablation) on the tumor immune microenvironment, proper patient selection, and the optimal timing of immunotherapy.

No HCC systemic therapy is currently used in adjuvant setting. Two large randomized trials of sorafenib at earlier tumor stages, the STORM trial (postablation or resection) and SPACE trial (post chemoembolization), failed to show clinical benefits (17). In contrast, immune checkpoint inhibitors (ICI) have demonstrated improved survival benefit in the adjuvant setting and in the advanced metastatic setting for melanoma and non–small cell lung cancer. While this has not yet been demonstrated in phase III trials for HCC, the ongoing CheckMate 9DX study (NCT03383458), a global randomized phase III study of adjuvant nivolumab versus placebo after hepatic resection or ablation, seeks to definitively answer this question. This study restricts patient eligibility to those with preserved liver function (Childs-Pugh class A) and tumors at high-risk of recurrence, and thus will exclude a substantial proportion of patients who may also benefit from effective adjuvant therapy.

Also being explored are ICIs in the neoadjuvant setting where they may offer certain advantages over adjuvant treatment. HCC tumors often recur from a micrometastatic or meta-chronous disease even after complete resection. Both adjuvant and neoadjuvant administration of an immune checkpoint inhibitor may eliminate micrometastatic disease, but neoadjuvant administration may be more effective because a robust immune response is dependent upon interactions between T cells, antigen-presenting cells, and tumor cells that are more likely to occur when a large volume of tumor is present. Successful response to neoadjuvant therapy in HCC may result in tumor downstaging and a larger liver remnant after resection. A report was shared at the workshop of a patient with locally advanced HCC who was successfully downstaged and underwent a margin-negative resection as part of an ongoing immunotherapy neoadjuvant clinical trial combining nivolumab with cabozantinib (NCT03299946). Similarly promising early results were presented at GI ASCO 2019, with 3 of 8 evaluable patients treated with neoadjuvant nivolumab and ipilimumab demonstrating pathologic complete response (18). The use of ICIs in the neoadjuvant setting also offers a tremendous research opportunity to better elucidate mechanisms of response and resistance in HCC. Systemic therapies in HCC are currently used only in patients with advanced HCC not amenable to locoregional therapies.

Equally important to the question of how and when to administer these agents is whether the combination of antiangiogenic therapy and immunotherapy is superior to monotherapy. Pre-clinical studies have suggested the potential for synergy between anti-VEGF- and anti–PD-1- therapies, and such combinations have shown promising response rates without excess toxicity. An update of a phase I clinical trial of atezolizumab and bevacizumab that was presented at the workshop showed an ORR of 32%. Similarly, preliminary results of a phase I study of lenvatinib plus pembrolizumab in patients with unresectable HCC were reported at ASCO 2018 with an encouraging response rate of 42%. These data led to phase III trials combining atezolizumab and bevacizumab (NCT03434379/IMbrave150), lenvatinib plus pembrolizumab (NCT03713593/LEAP-002), and cabozantinib plus atezolizumab (NCT03755791/COSMIC-312). The active comparators in these trials are sorafenib (IMbrave150, COSMIC-312) or lenvatinib (LEAP-002) and will not answer the question of PD-1 alone or anti–VEGF/PD-1 combination treatment in the first-line setting for patients with advanced stage HCC. Further studies are needed to understand the biological effects of VEGF on the immune microenvironment, and whether the available anti-VEGF therapies have distinct immune effects through other targets such as FGFR (lenvatinib) and AXL and Met (cabozantinib).

Another hurdle highlighted at the conference is that despite an improved understanding of the molecular heterogeneity of HCC, the disease continues to be treated primarily with a “one size fits all” model. Immune biomarkers used in other tumor types, such as PD-L1 staining or tumor mutational burden, have not reliably identified responders in HCC and are not used to inform clinical practice. Despite these drugs showing clear activity in HCC, without patient enrichment the randomized phase III studies carry the risk of not meeting their endpoints. Mutations in *Wnt/CTNNB1* have been proposed to confer resistance to immunotherapy, although further validation is needed (8). Similarly, the available multikinase inhibitors (cabozantinib, lenvatinib, regorafenib, sorafenib) have distinct molecular targets, but it is not known whether use of a more “personalized” TKI based on

biomarkers or putative oncogenic drivers within the tumor can optimize therapy. In one retrospective analysis, those with high levels of circulating FGF21 had longer survival with lenvatinib therapy than sorafenib, which is consistent with lenvatinib's potent inhibition of FGFR signaling relative to sorafenib (9). Such retrospective analyses can be hypothesis-generating and warrant prospective testing. Research is also needed to understand the interaction between etiology of cirrhosis and effects of viral hepatitis on outcomes and response to locoregional therapies, immunotherapies, and TKIs. Recent animal models of nonalcoholic steatohepatitis (NASH), specifically MUP-uPA mice, could present a reliable model of NASH-driven HCC, which has been used to evaluate HCC-targeting immunotherapies. Here, fructose-induced gut microbial alteration and inflammation led to NASH and HCC. A better understanding of the cross-talk between cancer cells and their microenvironment (including the microbiome) will be critical to identify new therapeutic targets for combination strategies.

Conclusion

In summary, HCC is the most rapidly rising cause of cancer-related death in the United States and a leading cause of cancer mortality worldwide. While we are encouraged by the recent successes, survival benefits remain modest. Greater progress in HCC will rely on advances and cross-disciplinary understanding of the complex biological mechanisms based on its etiologies, and precursor lesions such as chronic hepatitis, cirrhosis, and fatty liver conditions. Key questions are how much of these mechanisms remain distinct or come together to guide treatment approaches. Stronger proof-of-concept studies are required before committing to phase III development including the use of randomized phase II studies, rather than small single-arm studies. We also need to encourage scientifically based clinical trials that evaluate synergistic activity between locoregional therapies such as TACE and radiotherapy, targeted therapy, and immunotherapy for their ability to improve local and systemic cancer control. Contrary to current thoughts, TCGA genomics are not biased toward early, resectable HCCs, and apart from dietary aflatoxin intake, do not show strong effects of etiology (HBV, HCV, NASH) on genomic alterations. This raises further questions —why are the genomics not reflective of etiology? Despite the current paucity of biopsy and tissue samples, somatic mutation profiling remains important and feasible in HCC, may have major clinical utility, and should be systematically encouraged. Finally, new biomarkers, robust TCGA-driven animal models, with biomarker endpoints in clinical trials involving multiple modalities that include imaging, surgery, radiation, oncology, and hepatology are critical to tailor treatment choices and to develop and optimize new treatment strategies. Such randomized double-blind clinical trials that examine the multiple modalities (targeted therapeutics, radiation, surgery, transplantation), that are genomically-driven, tissue-based with biomarker endpoints are urgently needed.

Disclosure of Potential Conflicts of Interest

M. Yarchoan is a consultant/advisory board member for Eisai and Exelixis. A. Villanueva is a consultant/advisory board member for Guide-point, Fujifilm Wako, Exact Sciences, Nucleix, NGM Pharmaceuticals, and Exelixis. T. Karasic reports receiving a commercial research grant from Eli Lilly, Bristol Myers-Squibb, and Halozyme, has received other commercial research support from H3Biomedicine, Sirtex, Taiho, and Syndax, and has received speakers bureau honoraria from Pfizer. J.M Llovet reports receiving a commercial research grant from Bayer Healthcare Pharmaceuticals, Eisai, Bristol Myers-Squibb, and Ipsen, and is a consultant/advisory board member for

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