



Challenges in the Current Management of Hepatocellular Carcinoma

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Abstract

Management of hepatocellular carcinoma (HCC) is complicated. Barcelona Clinic Liver Cancer (BCLC) staging system is widely used in risk stratifying HCC. It is different from anatomic staging (TNM) used in other cancers and is based on the liver function (Child-Pugh Score) and performance status at diagnosis along with tumor characteristics like size/number of primary, vascular invasion, and distant metastasis. Guidelines proposed by various liver societies help the treating physician select first-line therapy, but there are many limitations to them. Lack of reliable biomarkers that give objective information to monitor the response other than alpha-fetoprotein or radiological response is hurting the management strategies. There are no ideal predictors for recurrence and residual microscopic disease, especially after locoregional therapy (LRT) like surgical resection, ablation, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and stereotactic radiation therapy (SBRT). Also, there is no convincing evidence to use adjunct therapy along with LRT in localized HCC. There is a need to identify the subset of HCC that would benefit from peri-procedural therapy. Recommendations for treating advanced HCC with macrovascular invasion is not uniform across the guidelines. Some propose LRT (TACE and/or TARE) or recommend systemic therapy only like tyrosine-kinase inhibitors (TKI) or Immune-checkpoint inhibitors (ICI). A considerable portion of patients have poor liver function (Child-Pugh Score C) at diagnosis. In this era of medicine, we should give them options other than supportive care, but unfortunately, it is the preferred option. This population needs special attention in trials. In current practice, there only 2-3 classes of drugs available like TKI, ICI, and vascular endothelial growth factor (VEGF) inhibitors. There is a need to explore more classes of liver-friendly drugs in treating HCC, and the enrolment of patients in clinical trials must be advised in the guidelines.

Keywords: *hepatocellular carcinoma, biomarkers, portal vein tumor thrombosis, adjunct therapy, immune-checkpoint inhibitors*

Background

Medical management of HCC is a daunting task, especially in the advanced or intermediate stages. In clinical practice, multidisciplinary tumor board consensus heavily influenced by locally available treatment options (like ablation, TACE, TARE, SBRT, and surgery) is followed rather than any specific guidelines. With very few options approved and no-good biomarkers to depend on, we are not able to get desirable results in managing these patients. It is high time we invest in designing effective management of complicated HCC patients with portal vein tumor thrombosis, poor liver function, and post-procedural therapy. There is a need to expand the class of drugs and non-invasive biomarkers in HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide, and its incidence is rising in recent years^[1,2]. Liver disease study groups around the world have proposed guidelines to manage HCC^[3-8]. They differ not only in staging the HCC but also in the preferred treatment options. Surgical resection, transarterial chemoembolization (TACE), ablation (radiofrequency or microwave), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), and external beam radiation therapy (EBRT) represent locoregional therapy (LRT). Systemic therapy is proposed in advanced stage HCC like macrovascular invasion (MVI) and distant metastasis. In early-stage tumors, they might be used in patients with poor liver function based on Child-Pugh Score (CP) or performance status (PS).

Aim of the review

The majority of the patients who present to medical oncologists are unresectable cancers ranging from intermediate to terminal stages with limited options available to make a meaningful difference. In this review, we shed light on the critical areas which need immediate attention in managing HCC, including lack of reliable biomarkers (for risk stratification and monitoring the treatment), effective adjuvant therapy strategies, inadequate systemic options, tumors with macrovascular invasion, and patients with compromised liver function.

Methods

This systematic review was performed in January 2021 using available databases: PubMed, Medline, Cochrane Library, Embase, and ClinicalTrials.gov. Unpublished data presented at international congresses as abstracts (American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO)) were also searched. The keywords used for the search were “Hepatocellular carcinoma” AND “management” OR “systemic

therapy” OR “biomarkers” OR “Child-Pugh C” OR “clinical trials” OR “macrovascular invasion.”

Discussion

Biomarkers in Clinical Practice

None of the guidelines proposed so far stressed using any biomarker for risk assessment or treatment recommendation. There are no prognostic markers in the current clinical practice to predict worse outcomes and monitor the response to treatment for HCC. Imaging (CT scan or MRI) and serum alfa-fetoprotein (AFP) levels are often used in monitoring the response to treatment are not always dependable. Diagnosis by imaging in the majority of cases removes the luxury of using traditional immunohistochemistry (IHC), or next-generation sequencing used to identify useful biomarkers like Her2 in breast cancer and MMR in colon cancer. As detailed in the table 1, biomarkers can be serum/blood-based testing [9-17], genetic data (IHC or sequencing,) [16-23], mutations in circulating tumor cells (CTC) [24], or treatment specific (sorafenib [25,26], TARE [27] or SBRT [28]). Most of these markers did not reach the clinical practice as of today.

Table 1: Biomarkers in HCC

Serum based	Platelet count (low) Mean plasma volume (high) HIV (seropositive) AFP/AFP -L3 Osteopontin Des-gamma-carboxy prothrombin (DCP) Glutamine synthetase Gamma globulins (in CPA with Cirrhosis) UL-16 binding protein 1 (ULBP1) in exosomes and as a free protein (> 2000 pg/ml) Anti-p16a, anti-CD25a and anti-FOXP3 IgG Exosomes - miR -122, miR-21
Tissue based testing. (IHC or sequencing)	Transketolase (TKT) Olfactomedin 2 (OLFM2) Acyl-CoA dehydrogenase (ACAD) Carnitine palmitoyltransferase 2 (CPT2) Adhesion G Protein-Coupled Receptor B1 (ADGRB1) Twist Family BHLH Transcription Factor 1 (TWIST1) Glutamine synthetase Glypican 3 General stress protein, Enhancer of zeste homologue 2 (EZH2) Heat shock protein 70 (HSP 70)
Mutations on CTC	TP53 Cyclin-dependent kinase inhibitor 2A (CDK2NA) Telomerase Reverse Transcriptase (TERT), Catenin beta 1 (CTNB1) AXIN1 AT-rich interaction domain 1A (ARID1A) Apolipoprotein B (APOB) Splicing factor 3b subunit 1 (SF3B1)
Sorafenib related	Inter Leukin-17A Hepatocyte growth factor [HGF] Fibroblast growth factor [FGF] Vascular endothelial growth factor receptor-1 CD117 Angiopoietin-2
TARE related	Image response Segmental treatment
SBRT related	Child-Pugh score Portal vein tumor thrombosis

	Tumor size
	Tumor response

Tissue-based biomarkers can be identified by IHC (phenotypic), while the expression of the genes (genotypic) can be identified by sequencing or FISH. Identification of specific mutations in circulating tumor cells (CTC) technology can be used in risk stratifying at the diagnosis but also to monitor the treatment by following the mutational burden serially. Histopathology of HCC is often ignored, and its impact on outcomes is underrated. The latest classification of it into four types, steatohepatitic, clear cell, fibrolamellar, and scirrhous was proposed [29]. Combining this classification with biomarkers can aid a clinically significant classification of HCC. There is a need to study the effectiveness of each LRT on specific histology type.

Adjunct therapy

According to the Surveillance, Epidemiology, and End Results (SEER) database, the five-year survival rate of localized HCC (along with Intrahepatic Bile Duct Cancer) is a mere 34%, which is surprisingly worse than localized pancreatic cancer (39%). The prevalence of bile duct cancer is very low. It is safe to assume that the recurrence rate and survival rate of localized HCC are not as good as colon cancer or breast cancer, where adjuvant therapy is

standard in the majority of the cases. In another study, the 10-year survival rate was only 10% in patients who received just LRT, which is alarming [30].

Unlike breast or colon cancer, the available guidelines do not have enough pre or post-procedural options for the patients that receive LRT in HCC. We need to intensify the debate on adjuvant or neoadjuvant therapy in HCC. The first step in that direction is to identify the concerning risk factors for treatment failure and recurrence. A comprehensive system that utilizes the biomarkers (as mentioned above) along with traditional risk factors (of HCC) like liver function and pathological factors is needed for it. Even though there is some evidence of adding systemic therapy to TACE, most of the guidelines do not encourage it [31]. Autologous cytokine-induced killer (CIK) is used after LRT like surgery in some Asian countries, but it has not been studied in Europe or North America [32]. Table 2 gives a list of some of the adjuvant therapy trials after LRT, like resection and ablation, and if these trials are positive, it will open a door for us. This further emphasizes encouraging physicians to start clinical trials or enroll the patients in the available trials.

Table 3: Current trials in HCC with adjunct therapy

LRT	ClinicalTrials.gov Identifier	Interventional arm	Comparative arm	Phase	Primary outcome
Ablation	NCT04178642	Idarubicin-Lipiodol	None – Single arm study	II	Survival without recurrence in 1yr
RFA/Resection	NCT03383458	Nivolumab	Placebo	III	PFS
	NCT04102098	Atezolizumab + Bevacizumab	Active Surveillance	III	PFS
	NCT03867084	Pembrolizumab	Placebo	III	PFS & OS
	NCT03847428*	Durvalumab and Bevacizumab	Durvalumab + placebo & Placebo alone	III	PFS
TACE	NCT03608878	Adagloxad simolenin/OBI-821	Active Surveillance	II	PFS Time-to-intrahepatic total tumor volume progression
	NCT03592706	Autologous Immune Killer Cells	Active Surveillance	II/III	Change in tumor size PFS
	NCT04340193	Nivolumab + Ipilimumab (Arm A)	Nivolumab + Ipilimumab (placebo) (Arm B) & Nivolumab (placebo)+ Ipilimumab (Arm C)	III	TTTP will be assessed by BICR: Arm A versus Arm C OS Arm A versus Arm C
	NCT04268888	Nivolumab	No systemic treatment	II/III	OS - phase III primary outcome, TTTP – phase II outcome
	NCT04246177	Pembrolizumab + Lenvatinib	Placebo (oral & IV)	III	PFS per RECIST 1.1 OS
	NCT03778957	Durvalumab + Bevacizumab (Arm B)	Durvalumab + Placebo (Arm A) & Placebo (Arm C)	III	PFS – Arm B vs Arm C
TARE	NCT04541173	Atezolizumab + bevacizumab	No systemic treatment	II	PFS per RECIST 1.1
	NCT03099564	Pembrolizumab	None - Single arm study	I	PFS per RECIST 1.1
	NCT03033446	Nivolumab	None - Single arm study	II	ORR
SBRT	NCT03203304	Ipilimumab + Nivolumab	Nivolumab	I	Number of participants with adverse events
	NCT01730937	Sorafenib	Soragenib alone (No SBRT)	III	OS
	NCT03316872	Pembrolizumab	None - Single arm study	II	ORR
	NCT03482102	Tremelimumab + Durvalumab	None - Single arm study	II	ORR
	NCT02906397	Galunisertib	None - Single arm Study	I	Safety

	NCT04387695	Sorafenib + TACE	Only Sorafenib (no SBRT or TACE)	III	PFS
	NCT01730937	With Sorafenib	Sorafenib alone	III	OS
Surgery	NCT03916627 (neoadjuvant)	Cemipilumab	None- Single arm study	II	Significant tumor necrosis (STN) at time of surgery
Electroporation	ClinicalTrials.gov Identifier	Nivolumab	Single arm study	II	Local PFS

OS – Overall Survival; PFS – progression-free survival; RECIST 1.1 - Response Evaluation Criteria in Solid Tumors Version 1.1; TTP - Time to TACE progression; BICR - Blinded independent central review; STN - Significant tumor necrosis

Macrovascular invasion

MVI in HCC refers to invasion portal vein or hepatic veins by the tumor. It is seen in 20% of the new HCC patients, and close to 50% of the unresectable HCC without it at presentation will eventually develop it [33]. MVI is associated with a grim prognosis as it impairs the blood flow to (and from) the liver; increases the risk of tumor spread; makes the tumor unresectable and ineligible to transplant; causes portal hypertension and profound liver failure [33]. For PVTT, the location of tumor invasion is important, the main trunk or its branches (first vs second order vs beyond) as the efficacy of LRT like TACE or TARE may depend on it.

Almost all the guidelines favor using TKI in HCC with MVI, as there is strong evidence for it except with Ramucirumab (by posthoc analysis of the trials) [33]. In an MDTB approach, the use of LRT, especially TARE, is not uncommon, and the success of such procedures is debatable. In TACE, the hepatic artery is blocked, which may cause liver failure and post-embolization syndrome in patients with blocked hepatic or portal veins. It is effective in selected cases (with branch vessel thrombus) [33,34]. Survival advantage with TARE was found only in patients with CP A and branch vessel disease [33,35]. SBRT seems to have a good response than TARE (with Y90), but that did not convert into any survival advantage [36]. Surgery, including hepatectomy with en bloc vascular resection or thrombectomy, may be effective in possible cases [37]. As in KLCG guidelines, where TACE and EBRT combination is proposed, we need to start assessing the use of adjuvant and neoadjuvant therapy in HCC with VMI. A combination of TARE with Sorafenib was studied in a number of studies but not specifically in patients with MVI but in unresectable tumors [35]. Just as with SBRT, the response rate is good, but it did not translate to a survival advantage.

It is not clear if there is any impact on the outcome or if the approach should be different for the hepatic vein invasion compared to the portal vein. The reluctance to start TKI (with multiple undesirable side effects) and temptation to use TARE or TACE in the clinical practice is comprehensible, especially in healthy patients, but the evidence is not favorable for such an approach. Pending reliable prospective trials, the success of ICI should prompt its use with LRT in non-metastatic HCC with MVI. The timing of such a combination can be concurrent or sequential.

HCC with Child-Pugh C

Management of patients with poor liver function (CP C) needs attention too. Such patients are categorized as terminal stage irrespective of their pathological features and PS. Major trials for both systemic and local therapies traditionally excluded such patients leaving us practically with no options for their management. If transplant-ineligible, supportive care is advised across the guidelines.

In our study accepted for ASCO this year (as discussed above), the use of ICI in terminal stage patients was the prime reason for non-adherence to the guidelines (which suggested BSC). When we further analyzed those patients, seven (7/13) patients

were classified into that group due to CP C only, while the rest were due to PS. Four out of those seven (4/7) CP C patients were treated with ICI (3 Nivolumab & 1 Pembrolizumab). One had a partial response for close to 10 months while the other had stable disease for 5 months, and none of them experienced grade 3/4 adverse events [38]. There are two takeaways from this limited study, (a) close to 50% of patients had PR or SD for a good 4-5months; (b) ICI is tolerable in CP C patients. There are other studies in the literature which support the tolerability of ICI in terminal stages [39,40]. The evidence on the efficacy of ICI in patients with poor liver function is limited by the studies (both prospective and retrospective) done on them.

A strategy to support the patients in terminal disease with reasonable PS should include a multidisciplinary approach with hepatologists leading the way and interventional radiologist or endoscopist supporting the oncologist. In patients with low tumor burden and treatable causes like HBV or HBC, addressing the etiology may give more time for disease control. Managing complications of liver failure like ascites (with diuretics), hepatic encephalopathy (with lactulose), and variceal hemorrhage (with endoscopic management), duct obstruction by the tumor (with ERCP/stenting or external drains) may give a fighting chance to save the patients. Trials must start including this subset of patients. Such trials might help manage the patients who start with good liver function but worsens later secondary to increasing tumor burden or other non-tumor-related causes (like cirrhosis).

Systemic therapy

Systemic therapy was also a weak link in the management of HCC until Sorafenib got approved in 2008. In recent years there has been considerable progress in this front, and we have 2-3 classes of drugs available now – tyrosine kinase inhibitor (TKI), vascular endothelial growth factor (VEGF) inhibitors, and immune-checkpoint inhibitor (ICI). Current options for TKIs are Sorafenib, Lenvatinib, Regorafenib, and Cabozantinib [41-44]. Until recently, the only VEGF inhibitor used was Ramucirumab (in AFP > 400) [45].

Convincing evidence for ICI in the first line was given by IMbrave150 trial, where the combination of Atezolizumab and Bevacizumab did well against Sorafenib (Overall survival at 12 months was 67.2% vs 54.6%) [46]. In the Checkmate 459 trial, when compared to Sorafenib, nivolumab had a better objective response rate (ORR), more complete responses (CR), and fewer severe adverse events, but it did not reach the pre-determined median overall survival threshold. In the first trial on nivolumab for HCC. In Checkmate 40 (an open-label, non-comparative, phase 1/2 dose escalation and expansion trial), Sorafenib treated patients were added in the expansion phase. Durable ORR was seen in both sets of patients and was tolerable and better in the Sorafenib treated group [47]. It was approved for the first line in patients who may not tolerate Sorafenib. On the other hand, Pembrolizumab was tested in second-line testing after Sorafenib and was compared with best

supportive care (in keynote 240) [48]. The trial did not reach pre-specified targets but had good ORR.

It is disheartening to see limited systemic options in this deadly disease. There are many ongoing trials involving ICI or its combination with TKI (like HIMALAYA, LEAP-002, COSMIC-312, and CHECKMATE 9DW). In the earlier versions of guidelines, enrolling patients in clinical trials was encouraged but not in any latest guidelines. There is a need to encourage clinicians to enroll patients in first or second-line trials before a significant decline in their PS or liver function.

Conclusions

The approach to HCC with MVI and CP C needs attention as the available options (in the guidelines) are not encouraging. There is a need to design and enroll patients actively in trials involving adjunct therapies, especially in early/intermediate stage HCC. Biomarkers other than traditional AFP should be used in early diagnosis, predict recurrence and monitor therapy are needed for effective management of HCC.

List of abbreviations

Hepatocellular carcinoma (HCC)
Locoregional therapy (LRT)
Transarterial chemoembolization (TACE)
Transarterial radioembolization (TARE)
Stereotactic radiation therapy (SBRT)
Immune-checkpoint inhibitors (ICI)
Tyrosine-kinase inhibitors (TKI)
Macrovascular invasion (MVI)
Child Pugh Score (CP)

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Authors' contributions

Authors SJ, RV, SB and SS did the literature search and contributed to manuscript writing. AM supervised and reviewed the manuscript. All authors read and approved the final manuscript.

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