University of Texas Southwestern Medical Center
Internal Medicine Grand Rounds

"Management of Advanced Hepatocellular Carcinoma"

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I am a physician-scientist with a lab focused on the basic biology of liver regeneration and cancer. Our goal is to determine the genetic and cellular mechanisms of organ regeneration and to understand how these mechanisms contribute to cancer. One approach we use is to develop mice that possess enhanced organ regeneration in order to understand the upper limits of mammalian tissue repair. Given the liver's strong self-renewal ability in the face of injury, we expect that regenerative capacity will have strong and potentially targetable influences on carcinogenesis. 10% of my time is devoted to taking care of liver cancer patients at the Parkland Memorial Hospital Multidisciplinary HCC Clinic.

Purpose & Overview:
To review the systemic treatment of unresectable Hepatocellular Carcinoma.

Educational objectives:
At the conclusion of this lecture, the listener should be able to:
1.   Understand the challenges and goals of systemic therapy for HCC.
2.   Understand the history of clinical trials in advanced HCC.
3.   Define the standard of care for advanced, unresectable HCC.
4.   Overview of failed therapies tested in Phase 3 trials.

Management of Advanced Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the 6th most common cancer and 2nd leading cause of cancer-related death worldwide. In the US, its incidence has doubled over the past two decades due to the growing number of patients with hepatitis C virus (HCV) and/or non-alcoholic steatohepatitis (NASH) (1, 2). These and other etiologies of chronic liver injury such as hepatitis B (HBV) and alcohol abuse can ultimately result in cirrhosis and predispose patients to developing HCC (3). Patients with cirrhosis are at high risk for developing HCC with a 3-8% annual incidence rate; over 90% of HCC in the U.S. occur in the presence of cirrhosis (3, 4). For these reasons, HCC is projected to surpass breast and colorectal cancer to become the 3rd leading cause of cancer-related death in the U.S. by 2030 (5). In parallel with its incidence rate, the mortality rate for HCC has increased faster than that of other leading causes of cancer death (6, 7).

BCLC Staging/Treatment Algorithm
The Barcelona-Clinic Liver Cancer (BCLC) staging classification divides patients into five stages (0, A, B, C and D). This is the system this is most frequently used to guide treatment decisions and it is the one we use at Parkland and UTSW. Stages 0 and A (very early and early) are curable by surgery, transplantation, or radiofrequency ablation (3). However, less than 15% of patients with HCC are diagnosed with early stage tumors, and the vast majority are treated with locoregional (intermediate or BCLC B) or systemic therapies (advanced or BCLC C). BCLC D stage patients are end stage and are only eligible for best supportive care. The majority of HCC patients present with advanced stage disease and limited treatment options. Here I will review systemic therapy for non-surgical patients who are also not eligible for locoregional therapy.

Why systemic therapy is challenging for HCC
There are several HCC specific challenges that make the clinical science and practice of systemic treatment difficult. Patients not only have a difficult to treat cancer, they are also suffering from advanced liver disease/cirrhosis. Cirrhosis therapies are targeted toward common complications and symptoms such as hepatic encephalopathy, ascites, infection, and esophageal varices. Besides treatments for Hepatitis, there are no treatments directed toward increasing tissue function. The extent of liver disease as indicated by the Child-Pugh metric usually dictates what can and cannot be given therapeutically for HCC. It is often difficult to assess therapeutic efficacy since survival benefit is often dictated by the extent of liver disease and not by the therapeutic response of the cancer. Most often the cause of death is a mix between advancing tumor growth and declining liver health. Chemotherapy is also not well tolerated by liver disease patients. HCC is also thought to be a chemotherapy-refractory cancer, although this is more of a hypothesis than a fact. Lack of efficacy could be due to the fact that liver disease patients have not been given higher doses of chemotherapy, and also, few randomized clinical trials have been performed with cytotoxic chemotherapies in HCC. In addition, clinical trials have occurred in very distinct patient populations involving disparate kinds of cancer, metabolism, and etiologies of liver disease. Asian studies tend to be in young patients with well-compensated HBV cirrhosis, while western patients are typically older and have alcoholic or HCV based cirrhosis. Clinical trial results from one continent might not be completely relevant to patients on another continent. For example, phase 3 trials of Sorafenib in the western and eastern hemispheres showed quantitatively different levels of benefit.

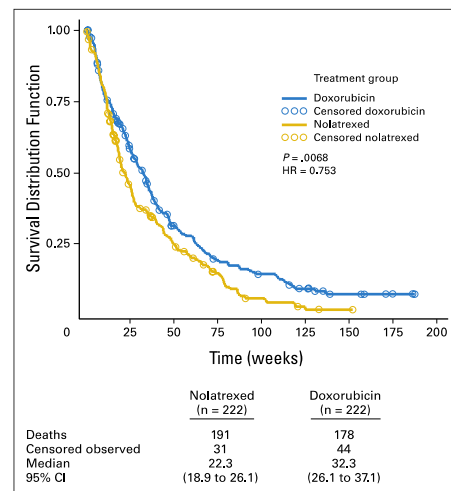**Systemic cytotoxic chemotherapy options**
Overall, cytotoxic chemotherapy has not been terribly successful for advanced HCC. No regimen has emerged as a true winner, and only a few randomized trials have been conducted. There is debate as to whether or not chemotherapy should even be used in real practice. Our

centers do not routinely use cytotoxic chemotherapy for advanced HCC patients. Here, I will review the pertinent studies that have been done and I have tried to avoid discussing small trials with less than 100 patients. Unless the magnitude of effects are large, these small trials (often uncontrolled) unreliable and are often overturned when subsequent trials are performed.

Monotherapy. Doxorubicin is the most studied chemotherapy agent in HCC, and results from many small trials have revealed that the response rate is approximately 20% (8-12). Lai et al. did perform a randomized clinical trial of single agent doxorubicin (n = 60) vs. supportive care (n = 46) that showed a median survival of 10.6 vs. 7.5 weeks (P = 0.036). A partial response was seen in only <10% of doxorubicin treated patients. It is unclear why the survival times were so low in this trial. Nearly a quarter of the doxorubicin patients suffered from infection and cardiotoxicity related fatalities, forcing the authors to conclude that this was not a particularly safe or efficacious approach.

In a North American/European trial, patients with unresectable or metastatic HCC were randomized to nolatrexed or doxorubicin (13). Enrolled patients had a Karnofsky performance status of >/= 60% and a CLIP score of </= 3. Median OS was not different (22.3 weeks for nolatrexed and 32.3 weeks for doxorubicin; p = .0068). The objective response rates were low (CR + PR was 1.4% vs. 4.0% for doxorubicin) and there was no significant difference in PFS. Grade 3 and 4 stomatitis, vomiting, diarrhea, and thrombocytopenia were more common in the nolatrexed arm. In contrast to the Lai trial, the doxorubicin arm was less toxic. Unfortunately, this trial does was not randomized against best supportive care, and thus we are left with some uncertainty about the real benefit of single agent doxorubicin in advanced HCC.

Doxorubicin vs. Nolatrexed (Gish et al.)

|	Nolatrexed (n = 222)	Doxorubicin (n = 222)
Deaths	191	178
Censored observed	31	44
Median	22.3	32.3
95% CI	(18.9 to 26.1)	(26.1 to 37.1)

Numerous other small trials evaluated single agent chemotherapy. For example, single agent capcitabine, gemcitabine, irinotecan and thalidomide have shown modest effects that have not been further examined against other regimens or BSC.

Combination chemotherapy. There have been numerous studies on combination regimens, but none were rigorously examined in large randomized studies. These studies mainly focused on response rates as measured by RESIST criteria. It is known from previous studies that therapeutic activity in the form of objective response often did not translate into survival benefits.

Agents	Response rates
Cisplatin + doxorubicin	18 and 49%
Cisplatin mitoxantrone 5FU	24 and 27%
Cisplatin epirubicin 5FU	15%
Cisplatin doxorubicin capcitabine	24%
low-dose infusional cisplatin plus infusional 5-FU	47%
Cisplatin capcitabine	6 and 20%
Gemcitabine cisplatin	20%
Gemcitabine + PEG liposomal doxorubicin	24%
Data taken from uptodate.com	

I will discuss one well-controlled Asian study comparing FOLFOX to doxorubicin. FOLFOX is a standard treatment protocol for advanced colorectal cancer. Modified FOLFOX4 vs. single agent doxorubicin (50mg/m^2 q3 weeks) was testing in 371 patients, 90% of which had HBV cirrhosis and advanced HCC (14). FOLFOX showed a slightly improved median survival that approached significance (6.4 versus 4.97 months, p = 0.07). FOLFOX had a higher objective response rate (8 vs. 3%). Surprisingly, the toxicity profiles were similar. A key problem with this study is that doxorubicin (50mg/m^2) was given at a relatively low dose in the control arm, which may have underestimated the survival promoting effect of doxorubicin.

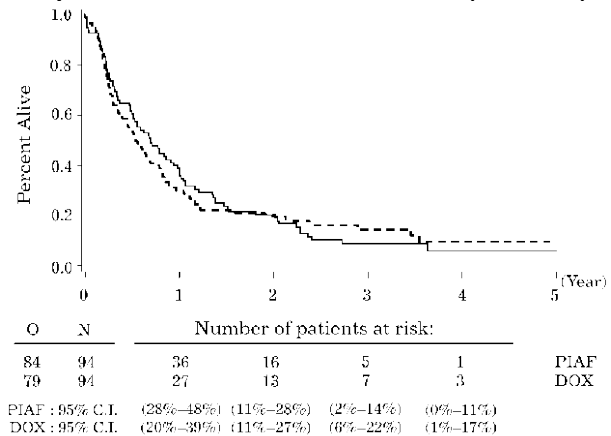**Kaplan-Meier for FOLFOX vs. doxorubicin (Qin et al.)**
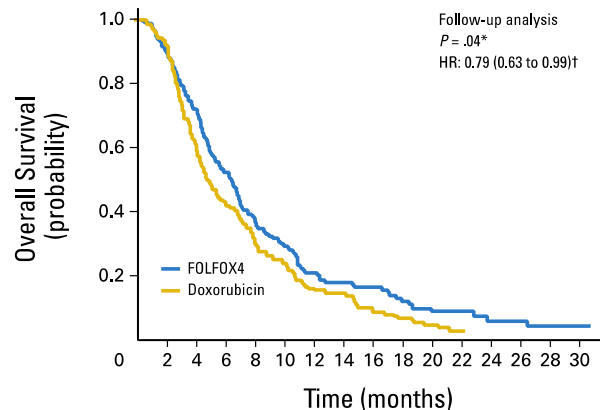
There was rigorous examination of another combination protocol called the PIAF regimen (cisplatin, interferon alpha, doxorubicin, and infusional 5-FU). PIAF is a toxic but active regimen that was compared to doxorubicin in 188 untreated patients (11). These patients were not selected based on performance status or Childs-Pugh, and they were randomized to doxorubicin monotherapy (60 mg/m^2 q3wks) or PIAF (cisplatin 20mg/m^2 on days 1-4, IFNa 5MU/m^2 SQ on days 1-4, doxorubicin 40mg/m^2 on day 1, and 5-FU 400mg/m^2 on days 1-4). PIAF showed higher objective response rate (21 vs. 11%) and OS (8.7 vs. 6.8 months, p = 0.83), but these were not statistically significant. The lack of selection for healthy patients may have compromised the significance, since patients with better liver function generally responded better to PIAF. Based on this study PIAF should not be given to HCC patients given high levels of toxicity and the insignificant survival benefit.

The big picture for cytotoxic chemotherapy in HCC is that although there have been objective responses associated with doxorubicin monotherapy, it has not been rigorously compared to best supportive care in selected populations of healthy patients. Many of these doxorubicin trials were small and not well controlled. Adding additional chemos such as in the FOLFOX4 or PIAF regimens did not increase survival in substantial ways, and one is left uncertain if the objective benefit associated with additional chemo is worth the toxicity for most advanced HCC patients who are already very sick. One could consider recommending weekly low-dose doxorubicin

Kaplan-Meier for PIAF vs. doxorubicin (Yeo et al.)

for patients who have failed or cannot tolerate sorafenib, but there is not strong clinical evidence for it, especially in the 2nd line setting. Additional chemos such as cisplatin + gemcitabine or PIAF might be tolerated for very healthy patients but in my opinion these should be reserved for rare cases, and potentially in patients with mixed cholangiocarcinoma/HCC histology, where there is little treatment data. There is very little rigorous data to support or refute chemotherapy recommendations outside of a clinical trial.

Hormone therapy has been unsuccessful
Many hormone targeting agents have been studied in advanced HCC, including tamoxifen, octreotide, megestrol, and lanreotide. None have been shown to work in definitive randomized trials (15).

Molecularly targeted therapy
Sorafenib (Brand name Nexivar) is the only approved standard of care systemic therapy for HCC. Sorafenib is an orally active small molecule tyrosine kinase inhibitor with multiple targets that is known to inhibit Raf kinase and VEGFR (16). It is unclear if these are the relevant targets in human patient HCCs since most data is from cell lines. The phase III SHARP trial showed a survival benefit over best supportive care alone (17). The SHARP trial was based in Europe, and randomized 602 patients with unresectable HCC (Child-Pugh A cirrhosis) to sorafenib (400mg PO BID) or placebo. Overall survival was improved (10.7 vs. 7.9 months, as was TTP (5.5 versus 2.8 months). Interestingly, there was only a 2% PR.

Sorafenib side effects and safety
One of the main advantages of sorafenib is the fact that the side effects are very manageable. In the SHARP trial, the only grade 3/4 adverse effects that occurred more than in the control group was diarrhea (8 vs. 2%) and hand-foot syndrome (8 vs. 1%), a skin reaction characterized by painful blistering and cracking. In practice, diarrhea is symptomatically treated with OTC anti-diarrhea medications such as immodium and lomotil. Protective moisturizing creams are used for the prevention of hand-foot skin reaction. Other side effects such as hypertension are monitored closely and treated if necessary. Liver toxicity in the form of hepatocyte liver damage with elevated transaminases is monitored at every visit. More rarely, PT/INR elevations or hyperbilirubinemia may occur. Less common side effects include: kidney toxicity, arterial thromboembolism, bleeding, cardiotoxicity, thyroid dysfunction, chest/face rash, itching, alopecia, toxic encephalopathy, muscle cramps, and muscle wasting.

The majority of patients with HCC have underlying cirrhosis that competes with progressive HCC as a major cause of morbidity and mortality. SHARP only involved patients with Child-Pugh A, so safety in patients with more significant liver disease was unclear. In non-HCC cirrhotics, the 2-year survival for patients with Child-Pugh A, B, or C cirrhosis were 90, 70, and 38% (18). There is not copious data on this, but sorafenib appears to be safe in CP B patients but is very unlikely to be effective in Child-Pugh C patients. In our practice at Parkland, we routinely treat patients who are Child-Pugh B, but it up to the doctor's discretion for those who are B8-9. Generally speaking, those with refractory ascites and encephalopathy are not treated.

It is unclear if the dose of sorafenib should be modified in patients with liver disease. The safety of sorafenib in patients with high AST or ALT was studied in a subgroup from the SHARP trial, and these patients tolerated sorafenib well (19). Patients with up to ≥1.8 times the upper limit of normal transaminases did not have increased toxicity. A phase I study suggested that a dose reduction to 200mg BID is required in those with a bilirubin 1.5-3x the upper limit of normal, and that the drug cannot be tolerated with >3x normal hyperbilirubinemia. Generally, we start patients at 200 mg PO BID and titrate up to 400 BID within the first 1-2 months, depending on signs, symptoms, and side effects. This allows us to monitor LFT changes during the first few weeks of treatment. The drug is not given to patients with Tbili of > 3. We do not prescribe sorafenib to patients with Child-Pugh C, who are given best supportive care and hospice.

Sorafenib does not seem to be as effective in Asians. A placebo-controlled phase III trial was performed on 226 patients with Child-Pugh A cirrhosis and no prior systemic therapy for HCC. Patients were randomized to sorafenib 400 mg twice daily or placebo (20). Overall

survival (6.5 vs. 4.2 months) and TTP (2.8 vs. 1.4 months) favored sorafenib, but the effect size was reduced. Hand-foot syndrome (11%), diarrhea (6%), and fatigue (3%) occurred with similar frequency as was seen in the SHARP trial. Both trials used the same eligibility criteria, but the SHARP trial's control group lived longer than the Sorafenib treated group in Asia. The Asian patients did have more advanced disease and worse performance status, so it is unclear if Asian patients or Asian HCC's are not as responsive to sorafenib. It could also be true that response differences are due to the differences in HCC etiology. Some subgroup analysis from SHARP suggested that HCV patients responded better than HBV or ETOH ones (21). OS differences were larger in patients with HCV-related cirrhosis (14 vs. 7.4 months) when compared to patients with HBV-related cirrhosis (9.7 vs. 6.1 months) or alcohol related cirrhosis (10.3 vs. 8 months).

Sorafenib + doxorubicin was examined in a phase II trial in which all patients got doxorubicin (60 mg/m^2 q3wks), and randomized to sorafenib 400mg BID or placebo (22). The combination resulted in a longer TTP (6.4 vs. 2.8 months) and median OS (13.7 vs. 6.5 months). The toxicity was not significantly worse with the combination, although 20% of patients on sorafenib + doxorubicin had a decrease in left ventricular EF. Unfortunately, this combination was not compared to sorafenib alone, so the answer to that question awaits completion of an ongoing phase III trial.

Failed targeted trials
Since the SHARP trial, there have been a series of failed phase 3 trials in advanced HCC. These have been in the first or second line setting, and many of these have examined agents active in angiogenesis pathways. This topic has been thoroughly reviewed (23-25), so I will only briefly cover take home messages.

Sunitinib is an oral TKI that targets VEGFR, PDGFRs, KIT, RET, and FLT3. Phase 2 trials with Sunitinib suggested significant toxicity (myelosuppression, asthenia and hand-foot reaction). Despite a lower dose in a phase III trial comparing the lower daily dose of sunitinib to sorafenib (400 mg twice daily) in 1073 treatment naive patients with advanced HCC (26), interim data analysis showed that the sunitinib arm had reduced OS (7.9 vs. 10.2 months) and more toxicity.

The randomized phase III BRISK-FL study tested brivanib versus sorafenib (27). Brivanib is a dual inhibitor of VEGF and FGFR, which are molecular targets implicated in HCC. Noninferiority for brivanib versus sorafenib (n = 1,150) was not met when OS metrics were measured (hazard ratio, 1.06; 95.8% CI, 0.93 to 1.22). OS was 9.9 months for sorafenib (n = 578) vs. 9.5 months for brivanib (n = 577).

A phase III trial evaluated efficacy and tolerability of linifanib versus sorafenib in 1035 HCC patients without prior therapy (28). Linifanib is a potent inhibitor of receptor tyrosine kinases, VEGF, and PDGF. Median OS was 9.1 months on the linifanib arm and 9.8 months on the sorafenib arm (hazard ratio, 1.046; 95% CI, 0.896 to 1.221). TTP and ORR favored linifanib; safety results favored sorafenib.

The only trial that examined an agent in addition to the standard of care was the SEARCH trial. Unfortunately, the addition of erlotinib to sorafenib did not provide any survival advantage (29). 720 Child-Pugh A patients naive to treatment were randomized to sorafenib + erlotinib (n = 362) or sorafenib + placebo (n = 358). OS (9.5 both vs. 8.5 sorafenib alone; hazard ratio, 0.929; P = .408) was not significantly different, and neither was median TTP (3.2 v 4.0 months; HR, 1.135; P = .18). Toxicity was similar.

Axitinib is a second-generation tyrosine kinase inhibitor with activity against VEGFR1, VEGFR2, and VEGFR3. In a larger randomized phase II trial with 202 advanced HCC patients who had progressed on or could not tolerate sorafenib, Axitinib could not beat best supportive care (30). Median OS was not significantly different (12.7 vs. 9.7 months, hazard ratio 0.907, 95% CI 0.646-1.274).

EVOLVE-1 was a 2nd line randomized phase 3 trial comparing Everolimus, an mTOR inhibitor, to placebo in 546 Child-Pugh A patients with BCLC B or C HCC who progressed or could not tolerate sorafenib (31). The median overall survival was 7.6 months with everolimus (n = 362) and 7.3 months with placebo (n = 184), and this was again insignificant.

Ramucirumab is a recombinant antibody that serves as a VEGF receptor antagonist. In the randomized, double-blind, phase 3 REACH trial, 2nd line treatment with ramucirumab did not improve survival over placebo (32). Median OS for the ramucirumab group was 9.2 (n = 283) vs. 7.6 (n = 282) months (hazard ratio, 0.87; 95% CI 0.72-1.05; p = 0.14). The safety profile was manageable. Subset analysis suggested a benefit in high AFP patients, and ongoing trials are testing this.

Why have trials failed?
Many of the concepts I will discuss below are from a series of reviews (23-25). There are many potential reasons for these trial failures in HCC. Probably the most important reason is that the genetic drivers of HCC are not clear, especially in any given patient. Since patients are ill with some degree of liver disease, the toxicity of experimental drugs can obscure or even counteract positive anti-cancer effects. The trials themselves are problematic because they are basically all designed exactly like the SHARP trial. Predictive biomarkers were not used to maximize potential drug efficacy and thus patients who might uniquely respond were not selected for. Finally, the drugs themselves did not show evidence of strong anti-tumor potency.

Many phase II trials were not comprehensive enough to prevent ineffective drugs from getting tested in large phase III trials. Llovet says that liver toxicity needs to be better defined in phase II prior to phase III studies. Also, larger and more thorough phase II trials might reduce randomness and reveal a clearer toxicity profile, survival benefit or lack thereof. In these trials, secondary endpoints need to be separated out since metastases and PVT are very different outcomes that do not capture the diversity of the HCC natural histories. Moreover, TTP and OS often do not track together. This would indicate that OS might need to be an endpoint in phase II trials. In addition, HCC is in desperate need of more biomarker data to select subgroups that might be enriched for response or lack of response. An example of this would be the situation in colon cancer, where Cetuximab effectiveness is dependent on Kras mutational status.

Also, a more diverse portfolio of targets should be evaluated. As seen above, most of what was targeted was in the VEGF pathway, so comparing multiple angiogenesis inhibitors against each other might not be the best strategy to identify winning regimens. A major area of focus should be the WNT beta-catenin pathway, which is active in over 30% of HCCs. Currently, the MET inhibitors tivantinib and cabozantinib are being compared with placebo in phase III trials (33). Immunotherapy is also an intriguing area of study for HCC. Nivolumab is a humanized antibody that targets PD-1, thereby activating T-cell immunity against cancer cells (34). One phase I/II study included advanced HCC Child Pugh A or B patients whose disease had either progressed on sorafenib or were intolerant (El-Khoueiry et al., 2015). A report presented at ASCO 2015 included 47 patients, 75% of which had prior systemic treatment and 68% of which had previously received sorafenib. 8/42 patients had an objective antitumor response to nivolumab, and two were complete responses. 48% had stable disease and 7/8 responders had a

sustained response of more than 9 months. Again, this excitement must be challenged in larger phase III trials.

HCC is heterogeneous but we have not treated it that way

As phase III trials have indicated, HCC has been treated in a monolithic fashion. It is clear that there must be multiple kinds of disease subtypes because even before we perform high-resolution genetic analysis, clear clinical, radiographic, and histological differences between patients with HCC are observed (35). For example, infiltrative HCCs represent a subtype with aggressive behavior and a distinct radiological and morphologic appearance. Although the infiltrative pattern accounts for up to 18% of cases in the U.S., little is known about its behavioral or genetic characteristics, especially compared to the more common discrete, nodular morphology (35). Infiltrative HCCs are generally not surgically resected, so tissue from these cancers have not been obtained or studied. This is only one prominent example where we have a clear knowledge gap in a major type of HCC that appears to be clinically distinct.
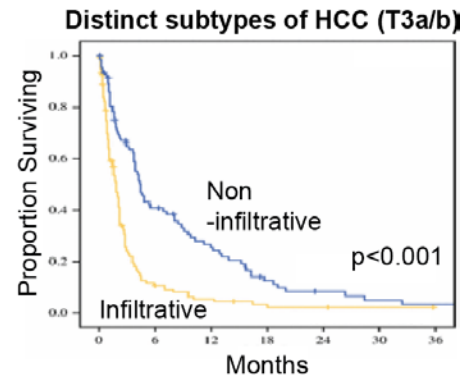
Survival of infiltrative and non-infiltrative HCC patients. This illustrates distinct and diverse biological entities that are staged identically (T3a/T3b).

We do not have tissue on advanced HCCs

Although infiltrative cancers are a obvious example of a very distinct advanced HCC subtype, a larger question is whether or not advanced HCCs overall represent simple progression from early cases or if these HCC populations are comprised of *distinct* biological entities with *unique* growth mechanisms, genetic dependencies, and differential sensitivity to systemic therapies. This would seem to be a major unknown because our suboptimal systemic therapies are directed toward these cancers, which have barely been examined.

A major reason for the lack of this information is because HCC diagnosis does not require biopsy confirmation but instead can be made using MRI or CT radiologic imaging alone. As a result, only surgical specimens from very early and early-stage HCC (BCLC 0 or A representing < 15% of all HCCs) have been deeply characterized. The Cancer Genome Atlas (TCGA) has analyzed over 300 HCC samples, but all are surgical samples (36). Thus, there are major gaps in our understanding of 1) HCC subtypes, particularly non-resectable subtypes, 2) genetic pathways worthy of targeting in advanced cases and 3) prognostic biomarkers for targeted treatments.

How would heterogeneity between early and advanced cases be investigated?

There have been countless numbers of tissue studies on HCCs in the past that have categorized gene expression and mutational profiles, so what has come of those studies and why has heterogeneity not been used to improve clinical trials? Genomics, like gene expression or any other biological characterization assay, has revealed additional heterogeneity in HCCs, but the next step is to connect this with biologic function and/or clinical outcomes. In general, the genetics heterogeneity of HCC has not been well correlated or associated with clinical or phenotypic characteristics such as therapy prediction. Ideally, patient response to therapies in failed III clinical trials should be connected to and correlated with genetic sequencing data from HCC biopsies, if they were collected prior to treatment. This kind of data has not been reported, although it is likely that it has been done to some extent.

Our HCC translational group has begun to take a basic science approaches to connect histology, genetic subtypes, and functional features of HCC. We have been characterizing distinct subtypes of HCC using mouse-human chimeric Patient Derived Xenografts (PDX). We have been trying to analyze and functionalize early and advanced stage HCC tumors with implantation of these tumors into immunodeficient xenograft models. There are only three published experiences with HCC PDX models, all of which are derived from Asian non-cirrhotic hepatitis B patients who underwent curative resection (37-39). These models do not represent the US HCC population, in whom >70% have HCV or NASH and >90% have cirrhosis. The successful delineation of tumor subtypes using PDX models could allow us to probe the genetic underpinnings of differences in behavior. This cohort of human HCC-bearing mice will also provide a platform to test experimental therapeutics.

Conclusions

There are many treatment options for those with early stage HCC, including surgical resection, transplantation, or ablation techniques. Intermediate and advanced HCCs are a more difficult challenge, given that patients have baseline liver cirrhosis that makes systemic therapies difficult to tolerate. Historically, cytotoxic chemotherapy has rarely been rigorously tested against supportive care. Though doxorubicin has activity against HCC, there is no evidence that single agent doxorubicin produces a clear survival benefit in advanced HCC patients. Based on the SHARP trial, sorafenib has become the clear standard of care therapy due to its limited toxicity and clear efficacy against placebo. Overall, systemic therapy in HCC leaves a lot to be desired. It is also possible that background liver disease reduces the number of patients that are able to tolerate truly efficacious agents. It is possible that the heterogeneity and diversity of genetic drivers makes HCC difficult to target. Linking descriptive genomic data to clinical outcomes and effective therapeutic modalities can potentially drive progress for systemic therapy.

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