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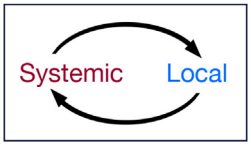

Combination and Optimal Sequencing of Systemic and Locoregional Therapies in Hepatocellular Carcinoma: Proceedings from the Society of Interventional Radiology Foundation Research Consensus Panel

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ABSTRACT

Hepatocellular carcinoma, historically, has had a poor prognosis with very few systemic options. Furthermore, most patients at diagnosis are not surgical candidates. Therefore, locoregional therapy (LRT) has been widely used, with strong data supporting its use. Over the last 15 years, there has been progress in the available systemic agents. This has led to the updated Barcelona Clinic Liver Cancer (BCLC) algorithm's inclusion of these new systemic agents, with advocacy of earlier usage in those who progress on LRT or have tumor characteristics that make them less likely to benefit from LRT. However, neither the adjunct of LRT nor the specific sequencing of combination therapies is addressed directly. This Research Consensus Panel sought to highlight research priorities pertaining to the combination and optimal sequencing of LRT and systemic therapy, assessing the greatest needs across BCLC stages.

ABBREVIATIONS

AE = adverse event, Atezo/Bev = atezolizumab and bevacizumab, BCLC = Barcelona Clinic Liver Cancer, c-TACE = conventional transarterial chemoembolization, DEB = drug-eluting bead, FDA = U.S. Food and Drug Administration, HCC = hepatocellular carcinoma, IRB = institutional review board, LRT = locoregional therapy, ORR = objective response rate, OS = overall survival, PBT = proton beam therapy, PFS = progression-free survival, RCP = Research Consensus Panel, RCT = randomized controlled trial, RT = radiotherapy, SBRT = stereotactic body radiotherapy, STRIDE = single tremelimumab regular interval durvalumab, TACE = transarterial chemoembolization, TARE = transarterial radioembolization

The 5-year survival rate for hepatocellular carcinoma (HCC) has been historically poor at 20% in the aggregate (1), with very few system options until 2017. Newer systemic regimens, featured namely in recent phase III clinical trials, IMBrave150 and HIMILAYA, have demonstrated improved survival and superior disease control, with decreased toxicity compared with sorafenib (2,3). Concurrently, there have been advances in techniques relating to intra-arterial locoregional therapies (LRTs) conferring improved survival in select populations as demonstrated by the subgroup analysis of the SARAH trial (4), DOSISPHERE-1 trial (5), and TRACE trial (6). Data are now emerging from studies investigating the combination of LRT with newer systemic agents for both intermediate- and advanced-stage disease (7). Some studies, such as LAUNCH, show improved survival benefit with early use of backbone systemic therapy (8,9). Determining whether overall survival (OS) is improved by the combined use of systemic therapy and LRT and in which patient populations could potentially represent a major development in the management of HCC.

The Society of Interventional Radiology (SIR) Foundation has identified the combination and optimal sequencing of LRT with systemic therapy in HCC as an emerging interventional radiologic research priority. SIR convened a Research Consensus Panel (RCP) with experts from diverse backgrounds who manage patients with HCC in their practice and have ample knowledge on the existing literature.

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METHODS

Panel Membership

On May 12–13, 2022, the SIR Foundation assembled an RCP with an intent to explore the combination and optimal sequencing of LRT and systemic therapy in the treatment of HCC. The panel was composed of a multidisciplinary group of 10 experts: 4 interventional radiologists (K.M., R.L., S.W., N.K.), 2 medical oncologists (H.L., R.F.), 1 hepatologist (M.K.), 2 hepatobiliary surgeons (R.J., P.C.), and 1 radiation oncologist (B.O.S.). There were also 3 members of the SIR Foundation present as well as a broad audience of observers representing clinical, academic, scientific, and commercial interests.

Agenda Methodology

The goal of the RCP was to provide an analysis of existing knowledge relating to the combination and sequencing of LRT and systemic therapy in HCC, while identifying knowledge gaps and prioritizing research needs. Two members of the SIR Foundation (D.L., L.T.) moderated the discussion, the senior author and first author. Each of 10 panelists produced a 15-minute presentation in their corresponding area of expertise, summarizing the current science in their field and most notable deficiencies. The topics addressed were centered on the following:

1. Current clinical algorithms for patient selection and available evidence supporting curative therapies
2. Literature review of intra-arterial and systemic therapies: identifying knowledge gaps
3. Review and discussion surrounding the use of combination regimens (LRT and systemic) and future prospects

The panelists were then asked to propose research questions to address the gaps and to rank them based on priority and feasibility. This was done using a modified Delphi Consensus format (10) in order to address the complexities of the multidisciplinary group and to reduce bias. Although the proceedings were open to the public and industry alike, only panel members were permitted to rank and vote. Owing to the wide breadth of the topics presented, the RCP article does not reflect the entirety of the proceedings. The article topics were selected on the basis of the presentation's relevancy to the voted on and selected research priorities at the culmination of the meeting. Institutional review board (IRB) approval was not required for summation of the content discussed in the RCP.

RESULTS

Current Clinical Algorithms: Filling in the Gaps

The treatment for HCC is challenging because of the presence of comorbid cirrhosis and variable tumor presentations. Recommendation of treatment may vary depending on societal guidelines (11–13). The Barcelona Clinic Liver Cancer (BCLC) staging system is commonly used, considering degree of cirrhosis and performance status, and is prescriptive of therapeutic options (14). Despite taking this into account, heterogeneity still exists within stages. As an example, the intermediate stage is broad and previously did not discriminate subsets (15,16). The updated BCLC now recommends earlier integration of systemic therapy in a subset that may fail LRT. This may be due to the BCLC B subgroup deriving a survival benefit compared with sorafenib in the IMBrave150 trial (14,17). However, the algorithm still lacks evidence-based guidance on the combination and sequencing of induction or adjuvant LRT. Other classifications have been proposed, such as the Kinki classification or Up-to-7 criteria (18–20), that also attempt to delineate subpopulations where LRT may fail and earlier systemic therapy may be appropriate, although with similar limitations (21). Contemporaneous practices have shifted the mindset from separate lines of therapies, to a model similar to colorectal cancer, where the therapies are integrated and potentially cyclical. In this setting, a multidisciplinary approach is advantageous to assess options for LRT, surgery, or transplant, longitudinally.

Intra-arterial Therapies

Transarterial chemoembolization (TACE) has longitudinally represented the standard of care for intermediate-stage HCC since demonstration of improved OS compared with best supportive care (22). The first prospective randomized controlled trials (RCTs) comparing drug-eluting embolic (DEE) TACE with conventional transarterial chemoembolization (c-TACE) (PRECISION V) demonstrated equipoise in tumor response, although with doxorubicin-related side effects reported as higher with c-TACE (23). A recent RCT compared DEE-TACE and c-TACE, conversely, revealing a significantly higher complete response rate with c-TACE. However, higher adverse events (AEs) were once again reported in the c-TACE arm (24). A meta-analysis of RCTs comparing TACE, both DEE-TACE and c-TACE, to bland embolization (transarterial embolization) also did not demonstrate superiority (25). The published OS for TACE ranges from 16 to 20 months and is approximately 30% at 3 years (26–28). There has been a lack of continued improvement in OS after TACE as a monotherapy over the past decade (6,12,27,29). This has allowed for newer transarterial therapies to be studied and compared with the historic standard of care.

Transarterial radioembolization (TARE) has been used across the BCLC spectrum for curative intent, intermediate disease, as well as in locally advanced cases with portal vein tumor thrombus (5,30,31). Recently, the Phase IIa TRACE trial compared TARE, using standard dosimetry, with DEE-TACE in unresectable tumors in early and intermediate stages. They reported significantly improved time to progression and OS with TARE. These results were

observed despite not all patients in the TARE arm receiving the therapy and, conversely, all patients in the TACE arm receiving the therapy with the intention-to-treat design. The TACE arm OS was lower than previously reported TACE cohorts, in the aggregate (6,32). However, when comparing this cohort with non-Asian studies, the OS was similar to previous data (12).

The possibility of ablative TARE,radiation segmentectomy (33), and boost dosing to tumor (5) have also recently been explored through modification of both radioactivity and specific activity of the microspheres (5,34). The prospective DOSISPHERE-1 and retrospective LEGACY studies demonstrated the importance of dosimetry (5,35), leading to updated dosimetry guidelines for tumors across the BCLC spectrum (36). Despite demonstration of the benefit of TARE in earlier stages (6,32,33,35), 3 RCTs have not shown survival benefit in advanced HCC (37–39). Among other criticisms, the trials did not take into account dosimetry as subsequent trials have (4,40). In post hoc analysis of the SARAH trial, patients who received at least 100 Gy (n = 67) exhibited longer survival than that among those who received less than 100 Gy (n = 54) (median, 14.1 vs 6.1 months; $P < .001$) (4). This highlights that dosimetry should be a methodologic focus on future, similarly designed, trials. It also suggests that if newer dosimetry and techniques are applied in BCLC B and C cohorts, the median OS may be improved.

The Use of Liver-Directed Therapies in the Setting of Metastatic and Advanced Disease

TARE was originally reported as safe in HCC with portal vein tumor thrombus owing to the lack of a macroembolic effect (41), thus inviting future study in patients with advanced disease. Three RCTs have compared TARE versus sorafenib, the previous standard of care. These studies were designed for superiority with a primary endpoint of OS. SIRveNIB and SARAH evaluated TARE versus sorafenib; SORAMIC compared the combination of TARE and sorafenib with sorafenib alone. TARE failed to demonstrate a statistically significant improvement in OS compared with sorafenib in all 3 studies (37–39). A specific trial assessing the effect of TARE versus sorafenib in a similar population (YES-P trial) was halted owing to slow accrual (42). Additionally, the STOP-HCC trial Phase III RCT has completed enrollment, which looked at TARE with glass microspheres and sorafenib versus sorafenib alone. The results of this trial have not yet been published (43).

There are several noted shortcomings of the published trials that might have contributed to lack of demonstrable survival benefit. First, 2 of the trials were conducted in geographical regions where access to TARE was limited except for clinical research indications limiting expertise. Second, a recurring feature of these studies was that fewer than 80% of patients allocated to the TARE arm received this treatment as an intention-to-treat study. Third, as mentioned earlier, dosimetry was not a focus in these studies and, therefore, they did not address the relationship between tumor radiation-absorbed dose and survival.

Over the past few years, several new effective systemic regimens have been established for the treatment of HCC showing superiority over sorafenib. Therefore, this is the new standard of care for patients with locally advanced HCC and macrovascular invasion. Future investigation with TARE should not only require optimized dosimetry but should also be compared or combined with the newer immuno-oncology regimens rather than sorafenib (42).

Radiotherapy and Abscopal Effects in HCC

A certain subset of patients with HCC may consider radiotherapy (RT) options such as stereotactic body radiotherapy (SBRT), proton beam therapy (PBT), or TARE. Historically, external beam radiation using 2-dimensional or 3-dimensional conformal techniques was ineffective owing to liver tolerance. Advances in RT, including intensity-modulated RT, SBRT, and PBT, now allow dose escalation while sparing healthy liver tissue, improving the therapeutic ratio (44–46). External beam RT may be beneficial for patients with HCC ineligible for other LRTs and in those needing to avoid certain procedural risks, such as catheterization, contrast, or general anesthesia (44). PBT has theoretical advantages over photon therapy, offering sharp dose falloff (Bragg peak), leading to a comparative reduction in mean liver dose. This gives PBT the potential to escalate dose (47,48) to those with compromised liver function (49,50) or advanced disease (49,51,52); however, high quality data are still lacking.

Immune checkpoint inhibitors show notable improvements in advanced HCC, although with response rates <50% (3,53,54). High-dose RT induces cancer cell apoptosis, releasing tumor fragments into the tumor microenvironment, potentially stimulating the host immune response (55). The hypothesis that ablated tissue acts as an in situ vaccine through tumor necrosis factor-α and T-cell stimulation stems from observed abscopal responses where tumor regression occurs outside the treatment field after local irradiation (56). In summary, combining immune checkpoint inhibitors and radiation for intermediate- and advanced-stage HCC holds promise, but further research is needed to demonstrate the activity and clinical impact of abscopal effects.

Evidence-Based Review of Systemic Therapies

In 2007, the SHARP trial established sorafenib as the first systemic therapy for advanced HCC, showing a 31% reduction in the risk of death (hazard ratio, 0.69; 95% CI, 0.55–0.87; $P < .001$) and improved survival from 7.9 to 10.7 months; similar results were reported in a companion

Asia-Pacific study (57,58). After a decade of limited progress in systemic therapy, starting in 2017, there was a paradigm shift in advanced HCC owing to multiple positive trials.

After numerous negative studies, the REFLECT trial demonstrated lenvatinib's noninferiority to sorafenib as a first-line agent, with a median OS of 13 months and an objective response rate (ORR) of 24% (59). However, this was quickly overshadowed by the IMBrave150 trial comparing atezolizumab and bevacizumab (Atezo/Bev) with sorafenib. Despite broad inclusion criteria, the Atezo/Bev arm showed an OS of 19.2 months versus 13.4 months in the sorafenib arm, with a tripling of ORR (30% vs 11%) (3,17). Owing to bleeding risk, some patients are ineligible to receive Atezo/Bev. Recently, the U.S. Food and Drug Administration (FDA) approved the dual immunotherapy combination regimen of tremelimumab and monthly durvalumab (single tremelimumab regular interval durvalumab [STRIDE]). Studied in the HIMALAYA trial, STRIDE showed improved survival over sorafenib (16.4 vs 13.8 months) and is considered another first-line therapy (2). There has been no head-to-head trial comparing Atezo/Bev versus STRIDE regimens.

Multiple second-line agents exist, but there is limited evidence supporting optimal sequencing because they were previously studied only after frontline sorafenib. This makes application difficult, given most patients are now considered for other agents as first-line. FDA-approved second-line treatments include regorafenib, cabozantinib, combination ipilimumab and nivolumab, pembrolizumab, sorafenib, lenvatinib, and ramucirumab in patients with elevated α-fetoprotein levels (>400 ng/mL) (53,60–65).

Combining and Sequencing of Systemic and LRTs: Knowledge Gaps

Synergistic effects between systemic agents and LRT have been explored in 4 types of sequential therapy within RCTs: (*a*) sorafenib-TACE (28,66), (*b*) lenvatinib-TACE (67,68), (*c*) ABC conversion therapy (69,70), and (*d*) sorafenib plus SBRT versus sorafenib alone (71).

TACTICS, a multicenter RCT, examined sorafenib + on-demand TACE versus TACE alone and showed improved progression-free survival (PFS) of 25.2 versus 13.5 months ($P = .006$) (66). However, SPACE and TACE 2 trials, also featuring combined sorafenib regimens, did not demonstrate a difference in endpoints, with more AEs in combined sorafenib/TACE groups (72,73). Lenvatinib backbone therapy with on-demand TACE has been validated by the TACTICS-L trail and more recently by the Phase III RCT LAUNCH trial, reporting a clear survival benefit in those who received the combination therapy in intermediate-stage HCC (8,74).

Patients with intermediate-stage HCC may also benefit from Atezo/Bev and curative conversion (ABC conversion), as demonstrated in proof-of-concept analysis (75). Combining surgery or LRT with systemic agents can optimize response, aiming for complete response as the therapeutic goal (69,70). IMbrave050 study results suggest integrating systemic therapies into earlier stages may improve recurrence-free survival (76).

In RTOG 1112, patients with BCLC B and C cancer were randomized to sorafenib plus SBRT versus sorafenib alone, with OS as a primary endpoint. The study closed early because of the standard of care change to Atezo/Bev affecting accrual and thus, could not meet its primary endpoint of OS. OS was documented as 15.8 versus 12.3 months in the combination cohort versus sorafenib alone, showing trends toward improved quality of life (71).

Although there are no published RCTs combining TARE with immunotherapy regimens, there are some early studies that suggest positive signal. An early Phase I/II trial demonstrated safety of TARE with single-agent checkpoint inhibitor, durvalumab, demonstrating high disease control rate in 24 patients (77). Another single-arm Phase II study combining nivolumab and TARE showed safety and tolerability (78). In contrast, only 14 of 41 patients completed both LRT and nivolumab combination therapy in a subsequent Phase II single-arm trial. The majority of dropout occurred because of tumor progression or AEs (79). To date, there are no available prospective data combining TARE with first-line, standard-of-care, immunotherapy regimens in populations with either intermediate- or advanced-stage disease to guide current practice, thus, making clinical applicability of these Phase II studies difficult. However, these studies serve as the basis for future RCTs.

Data supporting combination of LRT and first-line immunotherapy, are, however, on the horizon. There are 3 Phase II single-arm trials, beginning to recruit, combining TARE with durvalumab combinations (STRIDE). EMERALD-90, which is not yet recruiting, will be a prospective single-arm study evaluating PFS of durvalumab/bevacizumab after TARE. The ROWAN trial, enrolling in the United States and Spain, is recruiting patients with BCLC B and C disease to a single-arm of STRIDE + TARE and evaluating ORR. There is also a Chinese study actively recruiting to the same therapy arm, TARE + STRIDE, in metastatic disease. Of note, IMMUNOWIN is an RCT randomizing TACE + STRIDE versus TARE + STRIDE in those with BCLC B disease. The results of these studies could substantiate the initiation of Phase III trials addressing the top research priority.

Panel Discussion/Prioritization

After the presentations, the panelists submitted the current perceived gaps in knowledge (**Table 1**). The topics were distilled and voted on (**Table 2**). The panel acknowledged that the largest knowledge gap and most pressing research front was to evaluate effectiveness of radioembolization with systemic therapy in the setting of locally advanced HCC. The second priority identified was investigating the effectiveness of induction therapy with systemic agents,

Table 1. All Submitted Research Topics

Submitted Research Priorites
Randomized trial of TARE prior to resection for solitary HCC <8 cm in size in a hemiliver
Whole-liver TARE followed by ablation of viable tumor on diffusion MR imaging compared with best supportive care alone
TACE compared with TARE as neoadjuvant treatment for resectable HCC
TACE vs TARE for early- and intermediate-stage disease
Define the patient population for LRT in the setting of active systemic therapy
Randomized trial of early/intermediate-stage HCC treated with TARE with posttreatment dosimetry randomized to early intervention with additional liver-directed therapy based on concordance between suboptimal post-TARE dosimetry and early post-TARE imaging vs standard of care (3-mo follow-up with multidisciplinary tumor board discussion)
Randomized trial of advanced HCC with PVTT treated with combination immunotherapy + TARE vs combination ImT alone
Randomized trial of advanced HCC with PVTT treated with combination immunotherapy + SBRT vs combination ImT alone
What is the role of combination therapy (systemic + liver-directed) and what is the best combination to explore?
What are the baseline biomarkers that should preclude patients from receiving liver-directed therapy alone?
RCT of TARE plus Atezo/Bev vs Atezo/Bev alone in Child A, ECOG 0–1, locally advanced HCC (PVTT) or TACE unsuitable (beyond Up-to-7?)
Study looking at the adjuvant use of Atezo/Bev with TARE in PVTT
Identify radiomic and epigenetic factors prognosticating poor outcome of LRT in HCC
Prospective registry for radiographic curative intent therapies in lesions 3–5 cm in size
Sequence of systemic therapy and LRT
Biomarkers for selection of patients
Combining, sequencing, and harmonization of systemic and locoregional therapies
Role of systemic therapy and LRT in pretransplant/neoadjuvant setting
Role of LRT as an immune modulator with concomitant or sequential systemic therapy
Atezo/Bev in combination with TACE vs Atezo/Bev alone in TACE unsuitable intermediate-stage HCC
Atezo/Bev after SBRT/proton therapy vs Atezo/Bev alone (or SBRT/proton alone)

Atezo = atezolizumab; Bev = bevacizumab; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; ImT = immunotherapy; LRT = locoregional therapy; MR = magnetic resonance; PVTT = portal vein tumor thrombus; RCT = randomized controlled trial; SBRT = stereotactic beam radiotherapy; TACE = transarterial chemoembolization; TARE = transarterial radioembolization.

followed by LRT. Evaluation of tumoral morphologic features as predictors of response and PFS was identified as the final priority.

CONCLUSION

In conclusion, the top research priorities identified by this RCP clearly stress the need to determine the most effective combinations of LRTs and systemic therapies, for optimal sequencing, and to determine the tumor types receiving the most benefit. Although OS has recently been improved in the most advanced cases of HCC with newer agents, further progress by possibly combining LRT would be a major breakthrough in the treatment of HCC. Although research has been published since the conclusion of this RCP, RCTs addressing the top research priorities are still forthcoming.

Table 2. All Voted on Research Topics

Rank	Research Priority
1	TARE + TKI/IO in <VP3 PVTT in patients with CPA
2	Induction with systemic agents prior to locoregional therapy
3	Tumor morphologic feature studied as a predictor of progression-free survival
4	Prospective registry of curative intent therapies
5	Locoregional therapy in patients with borderline hepatic function
6	TARE as an adjunctive therapy in those eligible for surgical management
7	Locoregional therapy plus antiangiogenic agent (ie, bevacizumab) safety registry

CPA = child pugh A; IO = immuno-oncology; PVTT = portal vein tumor thrombus; TARE = transarterial radioembolization.

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