Pilot Study of Intrahepatic Artery Chemotherapy in Combination with Sorafenib in Hepatocellular Carcinoma

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Abstract. *Background/Aim: Sorafenib and chemoembolization of the liver (TACE) have both produced increased survival in hepatocellular carcinoma (HCC). Some patients cannot tolerate TACE due to portal vein thrombosis or risk of liver failure. In this pilot trial, we aimed to combine intrahepatic infusion (IA) of cisplatin or carboplatin with sorafenib for unresectable HCC. Patients and Methods: Patients with Child's A or early B received IA cisplatin or carboplatin every 6 weeks with oral sorafenib. MRI/CT scans were performed every 6 weeks. Results: Eleven patients were accrued. Of 10 evaluable patients, 6 had clinical benefit (4 partial responses for 2+, 3+, 8+ and 18 months, 2 minor responses). Two patients were down-staged enough for ablation therapy or liver transplant and remain free of disease for 32+ and 36+ months. Toxicity was generally tolerable. Conclusion: Preliminary results are encouraging and this combination may down-stage some patients with unresectable disease.*

Hepatocellular carcinoma (HCC) is the second-leading cause of death in the world amongst men (seventh amongst women) with an overwhelming majority being related to Hepatitis B and C infections (1). Despite its prevalence, few effective treatment options exist for patients diagnosed with this aggressive tumor; median survival is reported to be approximately 20 months (2).

Since HCC is usually confined to the liver, the focus for unresectable disease is on locoregional therapies such as radiofrequency ablation (RFA) or hyperthermia, cryotherapy, intra-arterial chemotherapy (IAC), transarterial chemoembolization (TACE), cyberknife radiosurgery, and radioactive drug infusion. Transarterial procedures (especially IAC and TACE) have been of particular interest because HCC is a highly vascular tumor with certain chemosensitivity. Both procedures were developed as ways to effectively deliver higher chemotherapy concentrations directly to the tumor itself and potentially reducing systemic effects. But, both have been shown to have antitumor effects (3-10). TACE has been preferred because the addition of embolization is thought to magnify cytotoxic effects when used with intra-arterial chemotherapy. There are, though, concerns of higher risk of hepatic failure with TACE (especially in patients with portal vein thrombosis, a relative contraindication), and there currently exists no clear evidence that the addition of embolization influences response rates or survival. One example is a recent study where TACE did not lead to higher response rates when compared to IAC (24% with TACE and 56% for IAC), but the study was a small and survival between the two therapies were noted to be similar (11).

Sorafenib has been considered the standard systemic therapy for advanced unresectable HCC (12, 13). With the promising results of sorafenib and IAC, the aim of this study was to evaluate safety and effectiveness of a multidisciplinary treatment approach with IAC in combination with oral sorafenib for patients with unresectable HCC. We also discuss issues and problems associated with regional chemotherapy, either by infusion or with embolization of the liver and future directions.

Patients and Methods

This was a phase II pilot study for patients who had been diagnosed with unresectable hepatocellular carcinoma chosen to undergo treatment with intra-arterial chemotherapy infusion (with either cisplatin or carboplatin) combined with sorafenib. This trial was supported by Bayer HealthCare (Whippany, NJ, USA) and Onyx Pharmaceuticals, Inc (South San Francisco, CA, USA).

Eligibility criteria included patients 18 years of age or older with a diagnosis of hepatocellular carcinoma (either biopsy-proven or with radiographic evidence consistent with HCC along with an AFP of at least 400 ng/ml). Other criteria included unresectable disease or non-surgical candidacy, Child-Pugh Class A or B (maximum 7 points on the Child-Pugh scale), bilirubin <3 mg/dl, AST/ALT <5-

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Key Words: Intrahepatic chemotherapy, sorafenib, hepatocellular cancer.

times the upper limit of normal, ECOG performance status of 0 or 1, and no hepatic encephalopathy at the time of diagnosis. Intra-arterial chemotherapeutic agent (cisplatin or carboplatin) was chosen at the investigator's discretion, based on parameters for white blood cell count, platelet count, and creatinine.

Each patient enrolled in the study began treatment with intra-arterial administration of either cisplatin (60 mg per square meter of body-surface area) or carboplatin (dose calculated to achieve an area under the curve [AUC] of 6). The drug of choice was dissolved in 200 ml of 0.45% normal saline and infused percutaneously via the intrahepatic artery supplying the tumor(s). The infusion time was approximately 30-45 min. This was repeated approximately every 6 weeks, up to 12 cycles, if tolerated. Initially, sorafenib (400 mg orally twice daily) was given in between IAC cycles but treatment protocol was revised after safety data was reviewed. Since no bleeding events were reported, the sorafenib dose was changed to daily continuously throughout IAC cycles. MRI or CT scans of the abdomen were done at the start of treatment and then every 6 weeks. Treatment response was determined per RECIST criteria.

Table I. *Baseline characteristics of 11 enrolled patients.*

Characteristic	N (%)
Age at diagnosis (years)	Median 65 (range=48-84)
Male sex	9 (82)
Child-Pugh class A	10 (91)
AFP level at diagnosis (ng/ml)	Median 23.9 (range=4.4-36,908)
Etiology of Liver cirrhosis	
Hepatitis C	7 (64)
Alcohol	1 (9)
Non-alcoholic steatohepatitis	2 (18)
Primary biliary cirrhosis	1 (9)
Prior treatments	
RFA	1 (9)
None	10 (91)

Results

Eleven patients were enrolled in the study. The median age was 65 years with most patients being of male sex, and with underlying Hepatitis C infection. The baseline characteristics of all patients are summarized in Table I. The median number of cycles of IAC was 2 (ranging from 1 cycle to 7 cycles) with 64% of patients completing at least 2 cycles of therapy. Only one patient had prior treatment for HCC (ablation therapy done 2 years prior) before enrollment into the study. Out of the 11 patients, 10 were evaluable since one patient died before first scan was done to assess response.

There were very few adverse events directly related with study treatment. There was one reported Grade 3 transaminitis after first IAC procedure, but event was transient and laboratory values returned to baseline within a few days. Most reported adverse events were Grade 1-2: asthenia, nausea/vomiting, hiccups, diarrhea, and transient transaminitis. There was only one patient where therapy (sorafenib) was held temporarily due to adverse events (diarrhea). Two patients had their infusional chemotherapy switched from carboplatin to cisplatin due to thrombocytopenia, most likely from underlying liver cirrhosis. There was one dose reduction (cisplatin) because of leukopenia. There were no omissions of the study treatment, but one patient had a treatment delay due to Grade 2 transaminitis, most likely related to liver cirrhosis rather than from the study treatment itself.

No patients withdrew from the study due to intolerable toxicity. Four patients withdrew due to progressive disease. One patient died during study participation from a pulmonary embolism. One patient developed hepatic encephalopathy after receiving two IAC procedures and therefore was withdrawn from the study. Two patients had to stop treatment due to bleeding: one patient developed rectal bleeding due to hemorrhoids while on anticoagulant therapy and the other developed esophageal bleeding from varices. None of these events were believed to be directly associated with study treatment, but rather to patient's underlying liver dysfunction.

Out of the 10 evaluable patients, 6 patients had clinical benefit from undergoing this treatment protocol. Four patients were able to achieve a partial response with progression-free survival for at least 2 months (2+, 3+, 8+, and 18 months); CT scans from two of these patients are shown in Figures 1 and 2, showing responses of one of their target lesions after therapy. Two patients had their cancer down-staged: one became a candidate for ablation therapy and the other underwent liver transplantation. These two patients have been disease-free for 32+ and 36+ months, respectively. Two other patients had minor responses/stable disease from treatment. Four patients had no response to therapy.

Discussion

Results of this pilot phase II study show that combined therapy with IAC and sorafenib is feasible for patients diagnosed with hepatocellular carcinoma who maintain good liver function. Of the evaluable patients that were enrolled, the disease control rate (CR+PR+SD) was 60% while the objective response (CR+PR) rate was 40%. Two patients were down-staged and became candidates for other therapies, one of which was a potentially curative treatment (liver transplant).

Importantly, toxicity was usually mild and potential side-effects due to TACE, such as major abdominal pain and severe liver toxicity were not seen in our study. But there are still many questions that remain about this multi-modality approach: 1) would TACE combined with sorafenib be a safe and more effective approach? 2) what is the correct dosing and schedule of the intra-arterial chemotherapy with sorafenib? 3) what is the optimal chemotherapeutic agent to use for intra-arterial infusion? 4) which patient population is this approach best suited for?

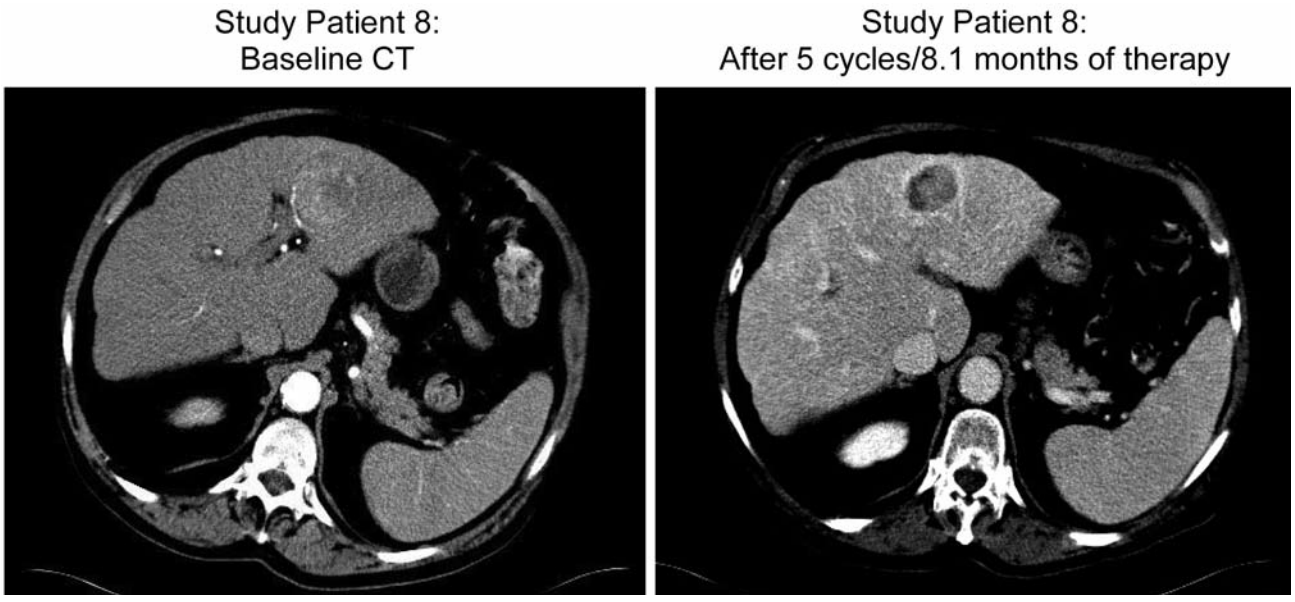

Figure 1. *Study Patient 8. Baseline CT showed large 5.4 cm lesion in the left lobe of the liver. After 5 cycles and more than 8 months of therapy, the lesion showed less enhancement.*

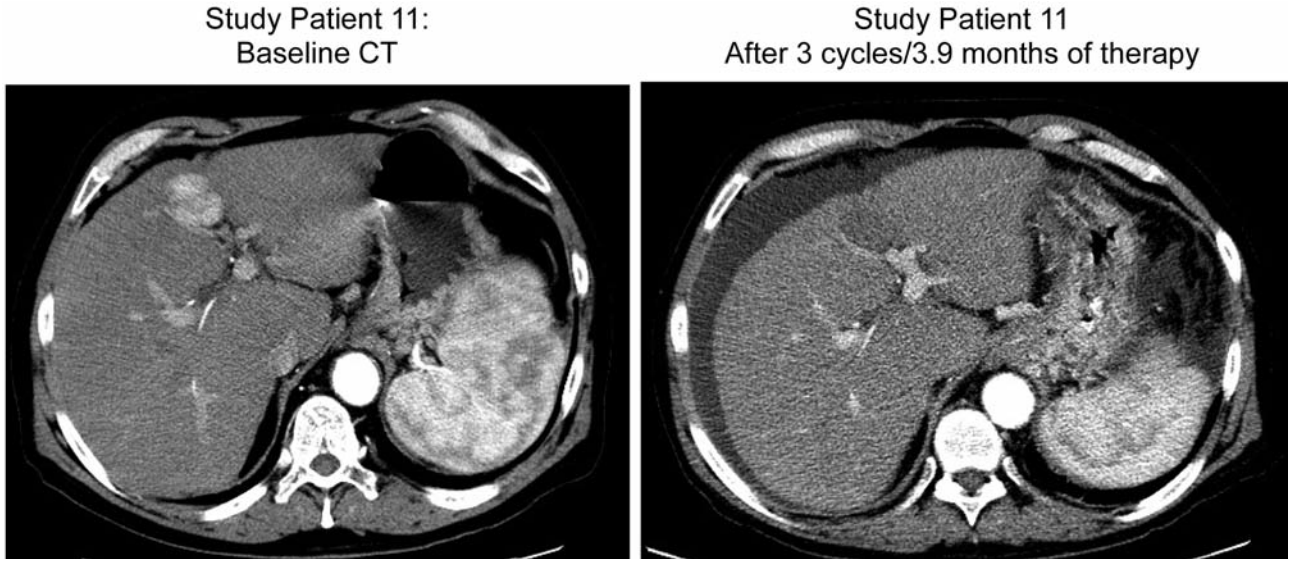

Figure 2. *Study Patient 11. Baseline CT showed a large 3.6 cm lesion in the left lobe of the liver. After 3 cycles and almost 4 months of therapy, the lesion shows no enhancement.*

IAC vs. TACE. Currently, there have been conflicting data about trans-arterial therapy. It is not known whether there is survival benefit nor which trans-arterial therapy (TACE or IAC) is safer or more effective. There exist two randomized trials that reported a survival benefit of TACE for unresectable HCC patients when compared to supportive care alone (14, 15). However subsequent meta-analyses were not able to confirm these results, both for TACE and IAC (although there were criticisms of the trials that were included in these meta-analyses). It is also unclear if there is an added benefit with the addition of embolization to IAC; very few trials have directly compared IAC to TACE. One study enrolled 37 patients to either IAC with cisplatin/5-fluorouracil or TACE (11). Response rates were reported as 56.3% with

IAC and 23.8% with TACE, suggesting a better anti-tumor effect with IAC. It was also observed that a subgroup of these patients with tumors staged as TNM Stage IV or had lesions larger than 5cm had higher survival rates with IAC compared to TACE. On the other hand, another study showed no difference in response rates between the two therapies (16). Again, neither study was able to show a difference in survival benefit, but direct comparison of these trials is difficult since each study used different chemotherapeutic agents and different embolization techniques.

Risks associated with each therapy also differ slightly. There is an assumption amongst clinicians that TACE carries higher risk for side-effects due to the embolization component. Side-effects that have been reported with TACE include: abdominal pain, fever, elevation of hepatic transaminases, ischemic liver abscess, bile duct injury, upper gastrointestinal bleeding, and damage to normal liver parenchyma that can lead to deterioration in liver function or liver failure (15, 17-21). Treatment-related mortality has been reported to range from 0 to 9.5%. In the above trials (11, 16), toxicity profiles between the two procedures were similar with the exception of significantly higher elevations in hepatic transaminases with TACE in one study (16). So it is still debatable if there is, in fact, a higher risk associated with TACE compared to IAC. Either way, the possibility of liver failure must always be a consideration with these procedures.

Multimodality therapy with sorafenib. Within the last few years, there have been many studies (22-29) looking at combination therapy with embolization techniques because of the effects of embolization on VEGF levels. As the vascular supply to the tumor is interrupted by embolization, tumor cells become more hypoxic, leading to up-regulation of hypoxia inducible factor-1α (HIF-1α). This will result in an increase in the levels of vascular endothelial growth factor (VEGF) and platelet-derived growth factor, which promotes angiogenesis and can enhance the proliferation of tumor cells (30-32). It has been observed that the VEGF levels are highest on the first day post-TACE and subsequently fall back to pre-TACE levels over the next 3 to 7 days (30). Sorafenib, when given after the embolization procedure, is intended to compensate for the increase in angiogenesis induced by the VEGF surge, which in theory, should translate to a greater, more prolonged antitumor effect compared to TACE alone.

Despite high expectations, studies using TACE with sorafenib have been inconclusive. One phase III study looked at 458 patients receiving sorafenib (or placebo) sequentially after TACE (33). This study failed to demonstrate improvement in TTP with the addition of sorafenib to TACE, although there were criticisms that the significant delay in the initiation of sorafenib (varied from 5 to 13 weeks after the last TACE procedure was completed) may have adversely affected its efficacy. Other studies did report overall response rates varying between 11% and 52% (24-28) but these trials were small so no definitive conclusions could be made.

With regards to the IAC/sorafenib approach, there is less concern on the VEGF surge since there is no embolization component. With combination therapy, it is hypothesized that there would be more of a synergistic treatment effect. But to date, there is very little clinical experience with this approach. This treatment approach was first studied in Japan where 5 patients were enrolled for IAC therapy with Cisplatin in combination with sorafenib (34). Each patient underwent one cycle of therapy (28 days of treatment) resulting in one partial response and 2 stable diseases. There were also case reports of two patients who underwent IAC/sorafenib who were able to achieve a response to therapy (35, 36).

Adverse effects of combined therapy. It is unclear at this time if combined therapy increases the risk of toxicity. Each modality of therapy itself carries its own risks. Most common adverse effects related to sorafenib were reported to be hypertension, hand-foot syndrome, rash, and diarrhea. Whereas, trans-arterial therapy has led to cytopenias, abdominal pain, transaminitis and less commonly, liver failure. However, studies-to-date using this multimodality approach have been inconsistent. One phase I study, which enrolled 15 patients to receive combination therapy with TACE/sorafenib, reported several grade 3/4 adverse events including diarrhea, hand-foot syndrome, abdominal pain, hyperbilirubinemia, and thrombocytopenia (22). Many of these patients required dose reductions and/or dose interruptions due to adverse events, with 21% of patients discontinuing therapy. Another study reported a significant number of grade 3/4 adverse events including cytopenias, anorexia, abdominal pain, diarrhea and neutropenic fever (27). There were 10 hospitalizations for complications from therapy with four therapy-related deaths. On the other hand, there are other reports (24-26, 28) using the TACE/sorafenib approach where toxicity profile was reported to be manageable.

These contrasting results are thought to be attributed to various treatment regimens. Each trial used different doses and types of the chemotherapeutic drugs and different schedules of sorafenib. The high toxicity in one study was largely attributed to the higher doxorubicin doses used for IAC (27). The continuous administration (given throughout all TACE procedures without interruption) of sorafenib with IAC may have also contributed to toxicity. Another trial also used a continuous dosing regimen for sorafenib (22). The other studies (24-26, 28) where toxicity was more manageable incorporated an interrupted schedule (where the administration of sorafenib was held 3 to 7 days before and after the TACE procedure).

For the IAC/sorafenib approach, studies are limited but toxicity seems to be more favorable. In one study the only reported severe adverse events were grade 3 hepatic transaminitis and grade 3 hepatic encephalopathy (although

these patients only underwent one cycle of therapy) (34). There is one case report (35, 36) of a hepatic arterial thrombosis during the IAC procedure, but this was thought to be related to vascular complications associated with the implantable port-catheter system (for delivery of IAC continuously over 5 days). In our experience, there were no thrombotic events associated with the IAC treatment.

Dosing and schedule of sorafenib. The optimal timing of sorafenib in relation to the trans-arterial procedure has yet to be determined. A randomized phase III study conducted in Japan evaluated the effectiveness of sorafenib therapy when initiated after TACE. Four hundred and fifty-eight patients were randomized to either sorafenib or placebo, with a median time to randomization of 9.3 weeks) (33). The study failed to show that the addition of sorafenib after TACE prolonged time to progression (the authors concluded that the negative result may be due to delayed initiation and low doses of the antiangiogenic therapy). Other trials have studied treatment protocols where sorafenib was integrated into the TACE schedule (either continuous dosing or interrupted dosing where antiangiogenic therapy was held around the times of the trans-arterial procedure) (22-28). For the TACE/sorafenib approach, the continuous dosing would theoretically be more ideal to counteract the VEGF surge triggered by the embolization (37). But this approach may be limited by toxicity of concurrent therapy. In two trials the higher toxicity of TACE/sorafenib may have been related to the continuous dosing (22, 27). Other recent trials utilized the interrupted dosing schedule due to concerns of TACE toxicity (23-26, 28). The interrupted schedule seems to be better tolerated but it is unclear if this was done at the expense of efficacy. Interestingly, a recent article suggested that the arterial blood supply of the tumor may be associated with the efficacy of sorafenib (38). HCC tumors with a good arterial blood supply benefited more than those with a poor arterial supply (38). This suggests that starting sorafenib prior to TACE could be more effective, but further studies are needed.

Since there is no VEGF surge in IAC, the timing of sorafenib would be less of an issue, theoretically. In our study, sorafenib was administered initially based upon the interrupted schedule (primarily due to concerns of bleeding risk associated with concurrent antiangiogenic therapy during an invasive procedure). Interim analysis done after the first year revealed no reported bleeding events and no grade 3/4 adverse events. Therefore, the treatment protocol was revised to change the administration of sorafenib to continuous. Both dosing schedules were tolerated very well and there were no reported bleeding events with the continuous schedule.

Optimal chemotherapeutic agent for intra-arterial administration. It is also not known which the optimal chemotherapeutic agent is for IAC and TACE. Many drugs have been used, including cisplatin, carboplatin, doxorubicin (including doxorubicin drug-eluting beads), and 5-fluorouracil (3-6, 39-46), but none has been shown to be superior to the others. Doxorubicin drug-eluting beads were developed to deliver higher doses of chemotherapy over a longer period of time without an increase in toxicity, which may be a more efficacious, tolerable option (47-49). In most of the trials of TACE/sorafenib, the drug of choice was doxorubicin. But the differences between chemotherapeutic agents have not been determined, so recommendations of a particular drug cannot be made. Our study used cisplatin and carboplatin due to better experience at our institution with these agents at the time of protocol creation. The only adverse event directly related to IAC was a transient transaminitis. There were also reported cytopenias but these not likely directly related to IAC therapy itself but did affect administration on a few occasions: one reported dose reduction (reduction of cisplatin due to leukopenia) and two changes in IAC agent (from carboplatin to cisplatin due to thrombocytopenia). Otherwise, these agents were well tolerated.

Patient selection. There is also a question if patients with portal vein thrombosis (PVT) could be candidates for this multidisciplinary approach. In the past, very few studies included patients with PVT due to a presumed higher risk of hepatic failure after embolization. Since there currently is not enough safety data, PVT is still considered a relative contraindication for TACE. In contrast, there have been several studies and case reports that have demonstrated the safety and efficacy of IAC in patients with PVT (10, 50-57). And there have been other reports of portal vein revascularization with sorafenib monotherapy (58-60). Therefore, there seems to be good scientific rationale to using a combination of IAC with sorafenib as initial therapy for patients with PVT. There are two reports to date (34, 35) that describe patients with PVT who benefitted from IAC/sorafenib combination therapy without significant adverse events. One of which is a case report describing a better therapeutic response to combination therapy (compared to IAC alone), and also documenting portal vein revascularization (35). In the TACE/sorafenib studies described above, very few patients with PVT were included. One study did include 20 patients with PVT. These patients were able to tolerate and benefit from TACE (26). But, currently since safety data are limited, IAC (with or without sorafenib) may be a safer option for patients with PVT.

IAC has also been the therapy of choice for HCC patients with co-morbidities and diminished performance status due to safety concerns from embolization procedures. Another consideration is the use of IAC/sorafenib in patients with multifocal, bi-lobed disease where embolization would not be feasible (simultaneous embolization of both lobes would put the patient at risk for

acute liver failure) or would be too risky. If IAC/sorafenib is shown to be easily tolerated, it may be possible to extend this approach for patient populations where TACE is currently considered a contraindication.

Most recent studies. There are several ongoing trials at this time using TACE/sorafenib (61), many of which are summarized in a review article published in 2013 (62). The two largest ones include the Eastern Cooperative Oncology Group (ECOG) 1208 trial and the Sorafenib or Placebo in combination with Transarterial Chemoembolization (SPACE) trial (62). The SPACE trial is a phase II study examining TACE using doxorubicin-eluting beads in combination with continuous administration of sorafenib (*versus* placebo). Although preliminary results were presented in ASCO 2012 showing that the TACE/sorafenib combination therapy met its primary endpoint of improving TTP, as well as demonstrating good tolerability (63); however, final published results showed no improvement in time to tumor progression (64). There are also other studies looking at other combination therapy such as radioembolization in combination with sorafenib (65, 66). TACE in combination with bevacizumab (another antiangiogenic agent) has been evaluated in a randomized phase II trial (67). No improvement in radiologic tumor response or overall survival was noted in the combination arm which produced more severe and even lethal septic and vascular side effects (67).

Brivanib, a selective dual inhibitor of vascular endothelial growth factor (VEGF) and fibroblast growth factor, did not improve overall survival when added to TACE (68). On the other hand, ginsenoside Rg3, a ginseng saponin which has multiple effects including down-regulating VEGF, promoting apoptosis and inhibiting proliferation and invasion of cancer cell, may prolong overall survival when added to TACE (69). In a meta-analysis, Kushen (Chinese patent medicine) injection may improve the tumor response to TACE (70) but randomized studies are needed to confirm this. Drugs that may not improve response or overall survival but instead may reduce complications from TACE include parecoxib (71). New studies showed promising markers for response to TACE, including interleukin-8 (72), microRNA-210 (73), serum miR-335 (74), circulating PAI-1 and serpine1 4 G/4G polymorphism (75) and novel imaging biomarkers (76). Finally, TACE can affect cellular immune function and regulatory T cells (77) and provides a rationale to use new immune therapies such as checkpoint inhibitors with TACE in HCC.

In summary, IA chemotherapy with cisplatin or carboplatin combined with sorafenib is feasible for unresectable HCC and toxicity of this treatment is generally tolerable. Preliminary results show encouraging activity and some patients can be down-staged for ablation or liver transplant. Further trials with larger number of patients with this combination is suggested, perhaps compared to TACE alone.

Acknowledgements

This trial was supported by a grant from Bayer HealthCare and Onyx Pharmaceuticals, Inc. Whippany, NJ, USA.

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Received March 7, 2016
Revised April 27, 2016
Accepted April 28, 2016