Temporary remission of advanced hepatocellular carcinoma in a patient treated with sorafenib therapy alone - A case report and literature review

Simran Elder¹ and Yixing Jiang*²
¹University of Maryland School of Medicine, Baltimore, USA
²Marlene and Stewart Greenebaum Cancer Center, University of Maryland Medical Center, Baltimore, USA

Abstract
Hepatocellular carcinoma (HCC) is a primary liver tumor which has been increasing in incidence over the past several years [1], and is the second leading cause of cancer death in the world [2]. Advanced HCC usually carries a poor prognosis. Over the past decade, systemic therapy for HCC has been evolving rapidly offering more therapeutic options and longer survival for those with incurable HCC. Here, we report a case of advanced HCC treated with single agent sorafenib and achieved complete radiographic response. In this article, we also provide a summary of current status of systemic therapy for HCC.

Case
A 57-year-old Asian male with a longstanding history of hepatitis C treated two years prior with Interferon as well as past history of heavy alcohol use and current smoking was evaluated by his primary care physician for right upper quadrant abdominal pain radiating to his back for four weeks. He was found on Computed Tomography (CT) scan to have a large mass in the right lobe of the liver suspicious for hepatocellular carcinoma, in conjunction with an Alpha-fetoprotein (AFP) of 78 IU/mL (previous value was reportedly 38 IU/mL). Unfortunately, the patient was then lost to follow up for 15 months due to social stressors. Upon return to care, further CT imaging showed multifocal hypervascular lesions involving both lobes of the liver, the largest being 11.5×7.5×15.7 cm with associated portal vein thrombosis, portal lymphadenopathy, and narrowing of the infrahepatic IVC (Figure 1). Biopsy of the largest lesion showed hepatocellular carcinoma in a background of cirrhosis.

Physical exam revealed normal vital signs, anicteric sclerae and no jaundice. He was noted to have a palpable liver 5 cm below the costal margin, and he did not have appreciable ascites. He was noted to have several tattoos, and otherwise had an unremarkable physical exam. The mass was deemed to be unresectable and not amenable to cure by transplant, thus the options of chemotherapy, chemoembolization and possible clinical trial participation were discussed with the patient. He was then referred to a Gastrointestinal Oncology specialist. It was determined that chemoembolization would not be ideal in the context of the patient's portal vein occlusion, and that unfortunately he was not a candidate for any available clinical trials at the time. His AFP was noted to rise to 387 IU/mL (Figure 2), with platelets of 104,000/mL, ALT 305 units/L, AST 579 units/L, alkaline phosphatase 426 units/L total bilirubin 1 mg/dL, WBC 2800/mL, hemoglobin 12 mg/dL, albumin 3.9 g/dL, creatinine 0.98 mg/dL. The option of Sorafenib was presented to the patient, which he agreed to and was initiated on Sorafenib 400 mg by mouth twice daily. One month later, the patient was noted to have a decrease in AFP (19.6 IU/mL) but developed hand foot syndrome as a result of Sorafenib. The Sorafenib was held briefly and restarted at 200 mg po TID. He tolerated this well, but 5 months later AFP was noted to have risen to 29.9 IU/mL. His CT, however, showed miraculous response with almost complete resolution of the previously seen large hepatic mass with normalization of liver architecture (Figure 3). This response was sustained for 15 months, at which time he was then found to have a new liver lesion on CT scan (Figure 4) with an AFP of 10.4 IU/ml. He was referred to interventional radiology and underwent transarterial chemoembolization (TACE) of this lesion, with good response on follow up CT scan two months later with stable AFP at 12.2 IU/mL, then 11.8 IU/mL. Sorafenib 400 mg by mouth daily was resumed. Two months later, he was noted to have a slightly increased AFP value at 28.6 IU/mL, with CT scan notable for a new hypervascular lesion in segment V (Figure 4). Sorafenib was continued and he was...

Figure 1 (a-c). CT performed 15 months after initial visit, before Sorafenib initiation, demonstrating involvement of both lobes of liver. The largest lesion is 11.5×7.5×15.7 cm with associated portal vein thrombosis, portal lymphadenopathy, and narrowing of the infrahepatic IVC
For many years, there was not a standard first line therapy for advanced HCC until 2008 when SHARP trial was published [3]. The SHARP trial was a phase III study to evaluate single agent sorafenib versus best supportive care in patients with advanced HCC. A total of 602 patients were randomized to receive sorafenib or placebo. The median overall survival (OS) in the sorafenib arm was 10.7 months while in the placebo arm it was 7.9 months. The moderate prolongation of survival time was statistically significant (95% confidence interval: 0.55-0.87; P<0.001). The partial response rate in sorafenib group was 2%. More than 70% patients experienced stable disease. The progression free survival was also superior in the sorafenib group (5.5 months vs 2.8 months). In 2009, Cheng et al published data of a phase III trial using sorafenib in Asian patients with advanced HCC [4]. The study accrued 271 patients with 150 assigned to sorafenib and 76 patients to placebo. The median OS was 6.5 months with sorafenib and 4.2 months with placebo (HR 0.68; 95% CI 0.5-0.93; P=0.14). It is noted that majority patients in SHARP study were Hepatitis C or alcohol related liver cirrhosis while the more than 70% patients in the latter trial were Hepatitis B positive. These two large phase III studies set the standard of care of first line therapy for advanced HCC worldwide.

Since the approval of Sorafenib, three tyrosine kinase inhibitors have been evaluated against Sorafenib to treat HCC in the first line setting. In 2013, Brivanib and Sunitinib were assessed in two large phase III studies. Brivanib is a dual receptor kinase inhibitor of VEGFR and FGFR. Phase II data showed that Brivanib achieved 11% objective response rate and 72% disease control rate in patients refractory to Sorafenib [5]. Brivanib as first line therapy demonstrated an OS of 9.8 months reported in a phase II study [6]. These encouraging results led to a randomized phase III trial comparing Brivanib to Sorafenib as first line therapy in advanced HCC, the BRISK study [7]. The results was rather disappointing. The median OS for Sorafenib was 9.9 months vs. 9.5 moths for Brivanib. The BRISK-P study compared Brivanib to placebo in patients who failed Sorafenib. More disappointingly, Brivanib did not improve OS over placebo [8]. The efficacy of Sunitinib was assessed in a large phase III study for first line therapy in HCC as well. The study enrolled total of 1074 patients worldwide. The median OS was 7.9 months in Sunitinib arm and 10.2 months in Sorafenib arm [9]. Sunitinib is associated with more severe adverse events. Linifanib is a VEGFR and PDGFR inhibitor. Linifanib showed significant activity in HCC in a single arm phase II study where a median OS of 9.7 months was reached [10]. Once again, Linifanib failed to demonstrate superiority to Sorafenib in a randomized phase III trial [10].

To improve the efficacy of Sorafenib, the combination of Sorafenib with other small molecules has been tried. Zhu et al reported a phase III study comparing Sorafenib with either Erlotinib or placebo in the SEARCH trial. A total of 720 patients were randomized in the study. The combination therapy neither improved OS (9.5 months in the combination arm; 8.5 months in the sorafenib arm) nor response rate (6.6% for the combination; 3.9% for sorafenib) [11].

After many failures, Lenvatinib was tested for first line therapy in a randomized, non-inferiority phase III trial [12]. Lenvatinib is a multi-kinase inhibitor of VEGFR, FGFR, PDGFR, RET and KIT. It has a proven role in the treatment of advanced renal cell carcinoma. A total of 954 patients were randomized to either receive Lenvatinib or Sorafenib. Lenvatinib achieved a surprising high response rate of 24%. However, the response rate (9.2%) in the Sorafenib arm was a bit higher comparing to the historical data. Median OS for Lenvatinib was 13.6 months and 12.3 months for Sorafenib. The toxicity profile for Lenvatinib is very similar to Sorafenib except for increasing dysphonia, hypothyroidism and vomiting with Lenvatinib, but overall, the medication is tolerable. The study met its primary objective of non-inferiority to Sorafenib. Patients with disease occupying more than 50% of the liver, bile duct invasion or main portal vein invasion were excluded from the study. One could argue that this study population is slightly healthier than that of previous HCC trials in the literature. Nonetheless, this pivotal trial set the new standard for first line therapy of advanced HCC (Table 1).

**Immune checkpoint inhibitors**

The FDA granted accelerated approval for Nivolumab (9/2017) and Pembrolizumab (11/2018), both monoclonal antibodies to PD-1, for advanced HCC progressed on the first line therapy based on phase II data. CheckMate-040 is a phase I/II dose escalation and

---

**First line therapy for advanced hepatocellular carcinoma**

For many years, there was not a standard first line therapy for advanced HCC until 2008 when SHARP trial was published [3]. The SHARP trial was a phase III study to evaluate single agent sorafenib versus best supportive care in patients with advanced HCC. A total of 602 patients were randomized to receive sorafenib or placebo. The median overall survival (OS) in the sorafenib arm was 10.7 months while in the placebo arm it was 7.9 months. The moderate prolongation of survival time was statistically significant (95% confidence interval: 0.55-0.87; P<0.001). The partial response rate in sorafenib group was 2%. More than 70% patients experienced stable disease. The progression free survival was also superior in the sorafenib group (5.5 months vs 2.8 months). In 2009, Cheng et al published data of a phase III trial using sorafenib in Asian patients with advanced HCC [4]. The study accrued 271 patients with 150 assigned to sorafenib and 76 patients to placebo. The median OS was 6.5 months with sorafenib and 4.2 months with placebo (HR 0.68; 95% CI 0.5-0.93; P=0.14). It is noted that majority patients in SHARP study were Hepatitis C or alcohol related liver cirrhosis while the more than 70% patients in the latter trial were Hepatitis B positive. These two large phase III studies set the standard of care of first line therapy for advanced HCC worldwide.

Since the approval of Sorafenib, three tyrosine kinase inhibitors have been evaluated against Sorafenib to treat HCC in the first line setting. In 2013, Brivanib and Sunitinib were assessed in two large phase III studies. Brivanib is a dual receptor kinase inhibitor of VEGFR and FGFR. Phase II data showed that Brivanib achieved 11% objective response rate and 72% disease control rate in patients refractory to Sorafenib [5]. Brivanib as first line therapy demonstrated an OS of 9.8 months reported in a phase II study [6]. These encouraging results led to a randomized phase III trial comparing Brivanib to Sorafenib as first line therapy in advanced HCC, the BRISK study [7]. The results was rather disappointing. The median OS for Sorafenib was 9.9 months vs. 9.5 moths for Brivanib. The BRISK-P study compared Brivanib to placebo in patients who failed Sorafenib. More disappointingly, Brivanib did not improve OS over placebo [8]. The efficacy of Sunitinib was assessed in a large phase III study for first line therapy in HCC as well. The study enrolled total of 1074 patients worldwide. The median OS was 7.9 months in Sunitinib arm and 10.2 months in Sorafenib arm [9]. Sunitinib is associated with more severe adverse events. Linifanib is a VEGFR and PDGFR inhibitor. Linifanib showed significant activity in HCC in a single arm phase II study where a median OS of 9.7 months was reached [10]. Once again, Linifanib failed to demonstrate superiority to Sorafenib in a randomized phase III trial [10].

To improve the efficacy of Sorafenib, the combination of Sorafenib with other small molecules has been tried. Zhu et al reported a phase III study comparing Sorafenib with either Erlotinib or placebo in the SEARCH trial. A total of 720 patients were randomized in the study. The combination therapy neither improved OS (9.5 months in the combination arm; 8.5 moths in the sorafenib arm) nor response rate (6.6% for the combination; 3.9% for sorafenib) [11].

After many failures, Lenvatinib was tested for first line therapy in a randomized, non-inferiority phase III trial [12]. Lenvatinib is a multi-kinase inhibitor of VEGFR, FGFR, PDGFR, RET and KIT. It has a proven role in the treatment of advanced renal cell carcinoma. A total of 954 patients were randomized to either receive Lenvatinib or Sorafenib. Lenvatinib achieved a surprising high response rate of 24%. However, the response rate (9.2%) in the Sorafenib arm was a bit higher comparing to the historical data. Median OS for Lenvatinib was 13.6 months and 12.3 months for Sorafenib. The toxicity profile for Lenvatinib is very similar to Sorafenib except for increasing dysphonia, hypothyroidism and vomiting with Lenvatinib, but overall, the medication is tolerable. The study met its primary objective of non-inferiority to Sorafenib. Patients with disease occupying more than 50% of the liver, bile duct invasion or main portal vein invasion were excluded from the study. One could argue that this study population is slightly healthier than that of previous HCC trials in the literature. Nonetheless, this pivotal trial set the new standard for first line therapy of advanced HCC (Table 1).
Elder S (2019) Temporary remission of advanced hepatocellular carcinoma in a patient treated with sorafenib therapy alone - A case report and literature review

Systemic therapy for advanced hepatocellular carcinoma is evolving rapidly, and therapy should be tailored to the individual patient. For those with symptoms caused by cancer such as pain from a large tumor stretching the hepatic capsule, for whom a quick reduction of the tumor size is needed to palliate symptoms, Lenvatinib might be a good option as it produces higher response rates than Sorafenib. For those with autoimmune disease, anti-PD-1 antibodies should be used with caution. For those who experience disease recurrence after liver transplant, both Nivolumab and Pembrolizumab are currently being evaluated in Asia (Table 2).

**Table 1. Randomized phase III trials in advanced hepatocellular carcinoma**

| Trial name | Number of patients | Response rate | Median overall survival | Progression free survival |
|------------|--------------------|---------------|-------------------------|---------------------------|
| SHARP      | 602                | 7% PR and 71% SD sorafenib vs. 1% PR and 67% SD placebo | 10.7 mos sorafenib vs. 7.9 mos placebo | 5.5 mos sorafenib vs. 2.8 mos placebo |
| Cheng et al. | 271                | 3.3% PR and 54% SD sorafenib vs. 1.3% PR and 27.6% SD placebo | 6.5 mos sorafenib vs. 4.2 mos placebo | 2.8 mos sorafenib vs. 1.4 mos placebo |
| BRISK-PS   | 395                | 10% Brivanib vs. 2% placebo | 9.4 mos Brivanib vs. 8.2 mos placebo | 4.2 mos Brivanib vs. 2.7 mos placebo |
| Cheng et al. | 1074               | 50.8% Sunitinib vs. 51.5% Sorafenib | 7.9 mos Sunitinib vs. 10.4 mos Sorafenib | 3.6 mos Sunitinib vs. 3 mos Sorafenib |
| Cainap et al. | 1035              | 10% Lixinifib vs. 6.1% Sorafenib | 9.1 mos Lixinifib vs. 9.8 mos Sorafenib | 4.2 mos Lixinifib vs. 2.9 mos Sorafenib |
| SEARCH     | 720                | 6.6% Sorafenib+erlotinib vs. 3.9% Sorafenib+placebo | 9.5 mos Sorafenib+erlotinib vs. 8.5 mos Sorafenib+placebo | 3.2 mos Sorafenib+erlotinib vs. 4 mos Sorafenib+placebo |
| SARAH      | 467                | 19% SIRT vs. 12% Sorafenib had CR or PR | 8 mos SIRT vs. 9.9 mos Sorafenib | 4.1 mos SIRT vs. 3.7 mos Sorafenib |
| Kudo et al. | 1492               | 24.1% Lenvatini vs. 9.2% Sorafenib | 13.6 mos Lenvatini vs. 12.3 Sorafenib | 7.4 mos Lenvatini vs. 3.7 mos Sorafenib |

**Table 2. Immune checkpoint trials in advanced hepatocellular carcinoma**

| Trial name | Number of patients | Response rate | Median overall survival | Progression free survival |
|------------|--------------------|---------------|-------------------------|---------------------------|
| CHECKMATE-040 Phase I | 262 | 20% with 3 mg/kg | Not yet reached | 28% |
| KEYNOTE-224 Phase II | 104 | 17% | 54% | 4.9 mos |
| KEYNOTE-240 Phase III | 408 | Ongoing | Ongoing | Ongoing |
| Pishvaian et al. Atezolizumab+Bevacizumab phase IB | 103 | Ongoing | Ongoing | Ongoing |
| Ikeda et al Phase I | Ongoing | Ongoing | Ongoing | Ongoing |
| Phase Ib Nivolumab+Lenvatinib | Ongoing | Ongoing | Ongoing | Ongoing |

Conclusions

Systemic therapy for advanced hepatocellular carcinoma is evolving rapidly, and therapy should be tailored to the individual patient. For those with symptoms caused by cancer such as pain from a large tumor stretching the hepatic capsule, for whom a quick reduction of the tumor size is needed to palliate symptoms, Lenvatinib might be a good option as it produces higher response rates than Sorafenib. For those with autoimmune disease, anti-PD-1 antibodies should be used with caution. For those who experience disease recurrence after liver transplant, both Nivolumab and Pembrolizumab are currently being evaluated in Asia (Table 2).
Elder S (2019) Temporary remission of advanced hepatocellular carcinoma in a patient treated with sorafenib therapy alone - A case report and literature review

References

1. Patrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS, et al. (2016) Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol 34: 1787-1794. [Crossref]

2. 2019 Cancer facts and stats from American cancer society. 2019.

3. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, et al. (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359: 378-390. [Crossref]

4. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, et al. (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10: 25-34. [Crossref]

5. Finn RS, Kang YK, Mulcahy M, Polite BN, Lim HY, et al. (2012) Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 18: 2090-2098. [Crossref]

6. Park JW, Finn RS, Kim JS, Karwal M, Li RK, et al. (2011) Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 17: 1973-1983. [Crossref]

7. Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, et al. (2013) Brivanib versus sorafenib as first-line therapy in patients with unresectable hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 31: 3517-3524. [Crossref]

8. Llovet JM, DeCaens T, Raoul JL, Boucher E, Kudo M, et al. (2013) Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 31: 3509-3516. [Crossref]

9. Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, et al. (2013) Sunitinib versus sorafenib in advanced hepatocellular cancer: Results of a randomized phase III trial. J Clin Oncol 31: 4067-4075. [Crossref]

10. Toh HC, Chen PJ, Carr BI, Knox JJ, Gill S, et al. (2013) Phase 2 trial of linifanib (ABT-869) in patients with unresectable or metastatic hepatocellular carcinoma. Cancer 119: 380-387. [Crossref]

11. Zhu AX, Rosmorduc O, Evans TR, Ross PJ, Santoro A, et al. (2015) SEARCH: A phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 33: 559-566.

12. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, et al. (2018) Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 391: 1163-1173.

13. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, et al. (2017) Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 389: 2492-2502. [Crossref]

14. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, et al. (2018) Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 19: 940-952. [Crossref]

15. Stein S, Pishvaian MJ, Lee MS, Lee KH, Hernandez S, et al. (2018) Safety and clinical activity of 1L atezolizumab+bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). J Clin Oncol 36.

16. Ikeda M, Sung MX, Kudo M, Kobayashi M, Baron AD, et al. (2018) A Phase Ib trial of lenvatinib (Lenv) plus pembrolizumab (PEM) in patients with unresectable hepatocellular carcinoma (HCC). J Clin Oncol.

Copyright: ©2019 Elder S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.