Sorafenib, A New Treatment for Advanced Hepatocellular Carcinoma: The Preliminary British Columbia Experience

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ABSTRACT

OBJECTIVE: Hepatocellular carcinoma is the fifth most common cancer worldwide and is a direct consequence of chronic liver disease, most commonly viral hepatitis, and cirrhosis. Current therapies for localized disease include surgical resection, locoregional radiologic interventions such as radiofrequency ablation, transarterial chemoembolization, and in select patients, liver transplantation. Historically, systemic chemotherapy has been disappointing and is rarely offered. Sorafenib is a new oral multikinase inhibitor that in the most recent pivotal clinical trial has demonstrated a survival benefit of almost 3 months over placebo. Sorafenib is now covered by the province via the British Columbia Cancer Agency and this study aims to assess the preliminary BC experience with this drug.

METHODS: A review was conducted of all patients referred to the British Columbia Cancer Agency with a diagnosis of hepatocellular carcinoma and we performed retrospective chart review on 30 patients who had received sorafenib.

RESULTS: Overall median survival was 7 months, similar to the placebo arm of the pivotal trial. Discontinuation of medication because of intolerability and disease progression occurred in 23 patients and only 30% took 80% of the optimal dose for a median of 2.8 months. Compared to the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, the BC group consisted of more patients from an Asian descent and more patients with advanced liver disease.

CONCLUSION: These results underscore the significant differences between the perfect conditions of a clinical trial, compared to the "real world" of clinical medicine. Future follow-up review of the BC sorafenib experience is warranted.

KEYWORDS: *sorafenib, hepatocellular carcinoma, survival, BCCA, retrospective*

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for over 90% of primary liver cancers, and is the fifth most common cancer worldwide as well as the third highest cause of cancer-related death.[1] HCC largely arises from a background of cirrhosis and chronic liver disease, usually due to hepatitis B virus (HBV), hepatitis C virus (HCV), as well as alcoholic liver disease or nonalcoholic steatohepatitis. It is less commonly due to α-1 antitrypsin deficiency, autoimmune hepatitis or hereditary hemochromatosis.[1] While surgical therapies, such as resection and liver transplantation, or locoregional procedures, such as radiofrequency ablation, are potentially curable, only 30–40% of HCC in North America are discovered at an early stage.[2] However, even after careful selection of patients undergoing resection, Llovet *et al.*[3] found that 1-, 3- and 5-year probability of recurrence were 19%, 54% and 70%, respectively. HCC that is not diagnosed until it has reached an advanced symptomatic stage or has progressed despite locoregional procedures is associated with a 5-year survival of less than 10%.[4] One reason for this dismal prognosis is the limited availability of effective systemic chemotherapeutic agents.

The University of British Columbia, with its main teaching hospitals within the city of Vancouver, is in a unique position to undertake clinical research in the area of HCC. Chronic HCV is a strong contributor to HCC – while the prevalence of HCV in Canada is 0.8%, the prevalence of HCV in British Columbia is

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approximately 1.5%.[5] Spinelli *et al.*[5] contributed this difference to high rates of intravenous drug use in BC. Concurrently, BC has the greatest proportion of visible minorities in Canada (21.6%), the majority of whom are from Asia.[6] In China and Taiwan, 13% and 15% of the respective populations are chronic carriers of HBV, and immigration from highly endemic HBV areas results in increased rates of HCC in BC, especially because HBV contributes to approximately 75% of HCC cases worldwide.[6]

Sorafenib is a new oral multikinase inhibitor – studies suggest its anticancer activity is related indirectly to decreased tumor angiogenesis by blocking vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR).[7,8] It is related directly to the inhibition of tumor cell proliferation by blocking Raf-1 kinase, an essential step in the RAF/mitogen-activation protein (MAP)/ extracellular signal-regulated kinase (ERK) (RAF/MAP/ERK) pathway.[7, 8] Treatment for advanced HCC with sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals – Onyx Pharmaceuticals) was recently studied by investigators in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, a randomized double-blind, placebo-controlled trial.[2] In this trial over 600 patients, primarily from western countries, with advanced unresectable HCC and Child-Pugh A hepatic reserve[9] (see table 1), were randomized to receive sorafenib or placebo.[2] Sorafenib was associated with an almost 3 month improvement in survival (median 10.7 vs 7.9 months).[2] After a number of previous negative trials of chemotherapy in HCC, sorafenib represents the first anticancer drug in 30 years to show a statistically significant and clinically meaningful survival benefit in advanced HCC.[2]

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Table 1. Child-Pugh Classification Table.[9]

	Points assigned		
Parameter	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	< 34.2 µmol/L	34.2 - 51.3 µmol/L	> 51.3 µmol/L
Albumin	> 35 g/L	28 - 35 g/L	< 28 g/L
INR	< 1.7	1.7 - 2.3	> 2.3
Encephalopathy	None	Grade 1 - 2	Grade 3 - 4

A total score of 5 - 6 is considered grade A (well-compensated disease); 7 - 9 is grade B (significant functional compromise); and 10 - 15 is grade C (decompensated disease).

Based upon these findings, sorafenib became available for use in British Columbia (BC) in 2008 for patients with advanced HCC and Child-Pugh A status. It is noteworthy that BC was the first province in Canada to provide drug coverage for sorafenib, via the British Columbia Cancer Agency (BCCA) drug formulary. To date, over 30 patients with advanced HCC have been treated with sorafenib by the BCCA. This study describes the local experience of sorafenib use at the BCCA. The purpose of this study was to compare preliminary results on survival benefit at BCCA to that observed in the pivotal SHARP clinical trial.

METHODS

A review was conducted in 2009 of all patients referred to the BCCA with a diagnosis of hepatocellular carcinoma. Those who received treatment with sorafenib were selected for review. Retrospective chart review was performed and data was collected with respect to patient demographics and risk factors, laboratory values, tumor characteristics pre- and post-treatment, treatment regimen and response, and survival outcome. One cycle of sorafenib consists of 4 weeks and recommended dosing regimen for sorafenib is 400 mg twice a day, but dosing interval can be reduced in response to side effects. Patients were regularly seen by physicians at BCCA. Overall survival was determined from the start of treatment to the date of death by Kaplan-Meier methods. All analyses were conducted with a computer software package (SPSS, SPSS Inc, Chicago IL). This study was approved by the University of British Columbia Clinical Research Ethics Board.

RESULTS

Patients

Thirty patients were included in the BCCA study. Demographics and baseline laboratory values are summarized alongside patient information from the SHARP study in table 2.[2] The average age of patients, gender ratio, baseline laboratory values and treatments used before sorafenib in the BCCA study was comparable to the SHARP study.[2] Ethnicity was documented in the BCCA study; 77% of patients were non-Asian and 23% were Asian. In contrast, the SHARP study recorded the patient's region of origin (table 2), and included patients from Europe and Australasia (88%), North America (9%), and Central and South America (3%). The BCCA cohort had more patients with a combination of risk factors (alcohol use with chronic hepatitis B infection, for example) than the SHARP study. Although not all patients had enough data to calculate the Child-Pugh class (measure of severity of end-stage liver disease), 16% of the total number of patients were considered class B, more than the 5% contained in the SHARP study.[2] Similarly, 63% of the BCCA study had extrahepatic spread of HCC compared to 53% in the SHARP study.[2]

Survival and treatment compliance

Overall median survival was calculated to be 212 days or 7.0 months (figure 1). In the SHARP study, patients receiving sorafenib and placebo had an overall median survival of 10.7 (95% confidence interval: 9.4 - 13.3 months) and 7.9 months (95% confidence interval: 6.8 - 9.1 months), respectively.

Table 2. Patient demographics and baseline values from BCCA study and SHARP trial.[2]

	BCCA patients (n = 30)	SHARP (2): sorafenib arm (n=299)	SHARP (2): placebo arm (n=303)
Age - yr ± standard deviation	61.6±12.1	64.9±11.2	66.3±10.2
Male	26 (87%)	260 (87%)	264 (87%)
Ethnicity			
Non-Asian	23 (77)	Not stated	Not stated
Asian	7 (23)	Not stated	Not stated
Region - no. patients (%)			
North America	30 (100)	27 (9)	29 (10)
Europe and Australasia		263 (88)	263 (87)
Central and South America		9 (3)	11 (4)
Risk factors - no. (%)			
Hepatitis B only	3 (17)	56 (19)	55 (18)
Hepatitis C only	1 (6)	87 (29)	82 (27)
Alcohol only	8 (44)	79 (26)	80 (26)
Alcohol + B	3 (17)	28 (9)	29 (10)
Alcohol + C	2 (11)	49 (16)	56 (19)
Other	1 (6)		
Unknown	12		
Child-Pugh class - no. (%)			
A	16 (84)	284 (95)	297 (98)
B	3 (16)	14 (5)	6 (2)
Unknown	11		
Extrahepatic spread - no. (%)	19 (63)	159 (53)	150 (50)
Biochemical analysis			
Serum albumin (g/L) (median range)	40 (29 - 44) (n=19)	39 (27 - 53)	40 (25 - 51)
Bilirubin (µmol/L) (median range)	10 (4 - 64) (n=27)	12.0 (1.7 - 280)	12.0 (3.4 - 104)
Alpha-fetoprotein (ng/mL) (median range)	84 (1.4 - 2.4x105) (n=29)	44.3 (0 - 208x104)	99.0 (0 - 5x105)
Previous therapy* - no. (%)			
Surgical resection	19 (33)	57 (19)	62 (20)
Ablation	2 (7)	17 (6)	12 (4)
Chemoembolization	2 (7)	86 (29)	90 (30)
Radiotherapy	0 (0)	13 (4)	15 (5)

*some patients received more than one type of therapy. In the SHARP study[2] there was no significant difference.

At the time of analysis, 23 patients had discontinued treatment. Disease progression was the most common reason for discontinuation (15 patients) followed by adverse events (7 patients) which are similar findings to the SHARP study.[2] The patients in the BCCA study had a median duration of treatment of 2.8 months, with 30% of patients receiving more than 80% of the planned daily dose. This was less than the treatment compliance achieved in the SHARP study, where the median duration of

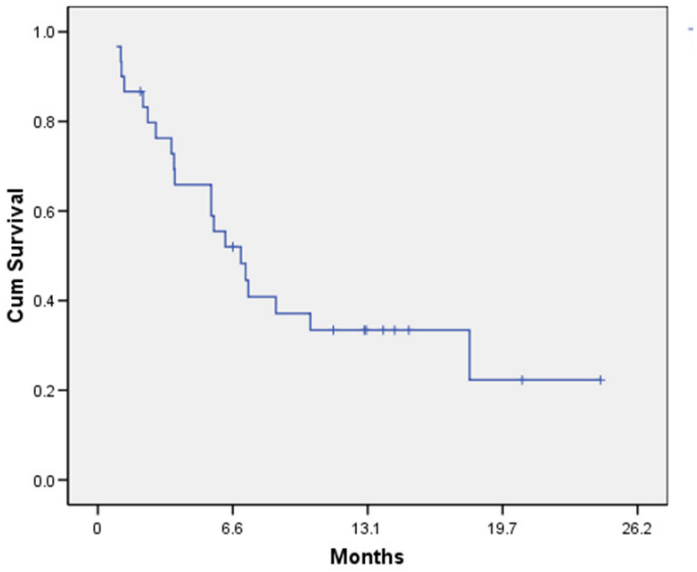

Figure 1. Kaplan-Meier Analysis of overall survival. Among 30 patients receiving sorafenib treatment for advanced hepatocellular carcinoma at the British Columbia Cancer Agency the overall median survival was 7.0 months.

treatment was 5.3 and 4.3 months in the sorafenib and placebo arm, respectively.[2] Additionally, 76% of patients in the treatment arm and 94% of patients in the placebo arm received greater than 80% of the planned daily dose.[2]

DISCUSSION

Often times, the experience in the clinical trial setting may not be entirely generalizable to the 'real-world' experience due primarily to patient selection and eligibility, and treatment compliance. In this study, the early experience and outcome of sorafenib treatment in BC patients with advanced HCC was compared to a phase III, multicenter, double-blind, placebo controlled trial to investigate its effectiveness in a local setting. Based upon our review, the two populations are similar in many regards, such as age, gender and baseline laboratory studies. An inherent difficulty with end-stage liver disease research is measuring the efficacy of treatment on the background of high mortality due to liver cell failure or portal hypertension.[10,11] Many studies, including the SHARP trial, choose to exclude cirrhotic patients beyond the Child-Pugh class A category to minimize this confounding variable. Of note, the BCCA study has a greater proportion of patients with Child-Pugh class B status, which may have impacted the assessment of sorafenib benefit and its tolerability or compliance.

Child-Pugh class was unavailable for 11 patients in the BCCA study. This was a limitation of the retrospective nature of the study, but highlights the importance of future accurate determination and documentation of relevant data prior to the initiation of sorafenib therapy for HCC.

The observed overall survival in the BCCA treated cohort was 7.0 months. This falls within the 95% confidence interval of the SHARP trial's placebo arm, specifically 6.8 - 9.1 months.[2]

While a direct comparison is not possible, factors to consider for this difference include a smaller sample size, a higher proportion of Child-Pugh Class B patients, a greater proportion of patients with extrahepatic spread, differences in patient ethnicity and differences in treatment compliance as clinical trial patients are typically followed by dedicated clinical trial nurses who monitor compliance via pill counts and patient diaries.

Despite the majority of HCC arising from the Asia-Pacific region,[6] the SHARP trial selected patients largely from European sites and some proponents have suggested that generalization of the success of sorafenib outside of this population is uncertain.[12,14] Taking 226 patients from China, Taiwan and South Korea, Cheng *et al*. was able to repeat the success of the SHARP trial in a similar phase III, randomized, double-blind placebo-controlled trial in what is sometimes called the "Asia-Pacific Trial".[12] They measured a statistically significant difference in overall median survival of 6.5 months (95% confidence interval 5.56 - 7.56 months) and 4.2 months (95% confidence interval 3.75 - 5.46 months) for those receiving sorafenib and placebo, respectively.[12] Interestingly, the overall median survival is comparatively less than the SHARP trial. While both trials show similar relative benefit with the addition of sorafenib as systemic chemotherapy for HCC, it is speculated that the overall prognosis for advanced HCC patients of Asian descent, particularly with underlying Hepatitis B disease have a more adverse prognosis than their western counterparts. As almost one-quarter of the BCCA cohort was of Asian descent, this variability in prognosis may be a factor contributing to the overall shorter survival observed in the BCCA experience.

The SHARP trial was able to achieve a substantially higher treatment compliance rate, with 76% of patients receiving more than 80% of the expected daily dose,[2] whereas in the BCCA cohort, only 30% of patients received more than 80% of the expected daily dose. Patients in the SHARP trial also received treatment for a longer period of time compared to the BCCA study (5.3 vs. 2.8 months). With treatment below target dosing for a shorter period of time, anti-HCC activity via inhibition of angiogenesis and cell proliferation would be diminished and possibly resulted in a lower overall median survival. While dose delays or dose reductions are entirely within the scope of appropriate clinical care, one way that the SHARP trial was likely able to avoid premature dose reductions was by strict adherence to protocol defined dose reduction guidelines. Such guidelines are difficult to enforce in practice, and typically, subjects on a clinical trial may be more accepting of higher levels of toxicity compared to clinical practice. In addition, ensuring compliance with an oral chemotherapeutic agent taken at home, such as sorafenib, can be more challenging than conventional intravenous chemotherapy given in clinic.

In the SHARP trial,[2] the Asia-Pacific trial,[12] and this BCCA study, many patients complained of adverse effects of sorafenib treatment. In the BCCA study, it was the reason for discontinuation in 23% of the patients. Similar to the side effects noted by the SHARP trial,[2] these included fatigue, hand-foot skin reaction, anorexia, diarrhea, nausea and hypertension. With severe adverse effects, this invariably leads to cessation of treatment. Future studies may be targeted at understanding sorafenib toxicity in the context of an individual patient's expression of biomarkers known to be related to HCC.

In summary, sorafenib represents a novel therapeutic option for patients with HCC. Challenges exist when attempting to extrapolate the clinical trial findings from the SHARP study to ascertain the impact of sorafenib in the real-world. Based upon our review of the early experience with implementation of sorafenib therapy for advanced HCC in BC, the overall survival of patients treated on the SHARP study appears to be more favorable than that observed in the BCCA experience. Attempts to improve patient selection, compliance and management of adverse events may optimize the impact of treatment for BC patients. Sorafenib patients will require careful selection in the future with regards to the degree of hepatic decompensation. Future follow-up review of the BC sorafenib experience is warranted to better understand the population-based impact of this novel therapy for patients with advanced HCC.

REFERENCES

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007 Jun;132(7):2557-76.
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008 Jul 24;359(4):378-90.
3. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999 Dec;30(6):1434-40.
4. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005 Nov;42(5):1208-36.
5. Spinelli JJ, Lai AS, Krajden M, Andonov A, Gascoyne RD, Connors JM, *et al*. Hepatitis C virus and risk of non-Hodgkin lymphoma in British Columbia, Canada. Int J Cancer 2008 Feb 1;122(3):630-3.
6. Cheung J, Lee TK, Teh CZ, Wang CY, Kwan WC, Yoshida EM. Cross-sectional study of hepatitis B awareness among Chinese and Southeast Asian Canadians in the Vancouver-Richmond community. Can J Gastroenterol 2005 Apr;19(4):245-9.
7. Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, *et al*. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006 Dec 15;66(24):11851-8.
8. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, *et al*. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004 Oct 1;64(19):7099-109.
9. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973 Aug;60(8):646-9.
10. Colombo M. Sorafenib in advanced hepatocellular carcinoma: a further step toward personalized therapy of liver cancer. Gastroenterology 2009 May;136(5):1832-5.
11. Kelley RK, Venook AP. Sorafenib in hepatocellular carcinoma: separating the hype from the hope. J Clin Oncol 2008 Dec 20;26(36):5845-8.
12. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. 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 2009 Jan;10(1):25-34.
13. Galle PR. Sorafenib in advanced hepatocellular carcinoma - We have won a battle not the war. J Hepatol 2008 Nov;49(5):871-3.
14. Scanga A, Kowdley K. Sorafenib: A glimmer of hope for unresectable hepatocellular carcinoma? Hepatology 2009 Jan;49(1):332-4.