Sorafenib in the treatment of advanced hepatocellular cancer

HOT SPOT

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Background

- Hepatocellular cancer (HCC) is the sixth most common cancer in the world
- Third most common cause of cancer-related mortality globally
- One of the few cancers that has incidence and mortality rates that are increasing in western countries
- 1,350 Canadians diagnosed with HCC in 2007
- Important risk factors include: Hepatitis B, Hepatitis C, all causes of cirrhosis, including alcohol abuse and metabolic diseases, as well as environmental toxins (e.g., aflatoxin)

Treatment options for advanced hepatocellular cancer

- Treatment is challenging as there are two disease entities: the malignant tumour with the propensity to invade underlying vascular structures and the cirrhotic liver
- Hepatic reserve, as indicated by the Child-Pugh classification, as well as disease stage, dictates therapeutic options
- 50% to 60% of patients present with advanced, inoperable disease, with a median survival of six months
- Systemic treatments using chemotherapy (doxorubicin or combinations) have not shown a survival benefit in patients with advanced HCC

Table One.

	Doxorubicin+ Sorafenib (n = 47)	Doxorubicin+ Placebo (n = 49)	*P- value*
TTP (months)	8.6	4.8	0.076
DCR (%)	81	57	
CR	0	2	
PR	4	0	
SD	77	55	
OS (months)	13.7	6.5	0.0049 (HR 0.45)

(TTP: time to progression; DCR: disease control rate;DCR=CR+PR+SD;CR:complete response; PR: partial response; SD: stable disease;OS: overall survival; HR: hazard ratio)

Sorafenib

- Sorafenib is a multitargeted, orally active, small molecule tyrosine kinase inhibitor. It blocks tumour cell proliferation by targeting the Raf kinase signalling pathway and has an antiangiogenic effect by targeting the intracellular portion of the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)

Evidence for Sorafenib for the treatment of HCC

Phase II Single Agent Therapy:

- International, phase II study in advanced HCC
- 137 patients—Child-Pugh A (72%); Child-Pugh B (28%)
- 41.6% achieved partial response, minor response or stable disease
- Most common grade three toxicities reported were fatigue (9.5%), diarrhea (8%) and hand-foot skin reaction (5.1%).

No grade four toxicities

- Comparison between Child-Pugh A and B patients revealed similar adverse events and dose intensity delivered between the two groups

Phase II Combination Therapy:

- Randomized phase II study, with 96 patients (see Table One)
- Doxorubicin plus sorafenib compared to doxorubicin plus placebo
- Most common grade three-four toxicities reported in the combination compared to the placebo arms were neutropenia (53% versus 46%) and fatigue (15% versus 15%), most certainly due to the doxorubicin
- Although this trial is strongly positive in favour of the doxorubicin plus sorafenib combination, it requires further study to determine if the benefit was owing to a positive interaction in the combination arm or to sorafenib alone

Phase III trials: SHARP

- The landmark SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial was the first phase III study to demonstrate an improved survival benefit for any drug in HCC (HR 0.69), positioning sorafenib as the new reference standard of care in advanced disease (see Table Two)

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- This was an international, double-blind, Phase III, multicentre, randomized trial comparing sorafenib to placebo in patients with advanced HCC. Eligible patients were not suitable for other local or curative therapies, had preserved liver function (Child-Pugh A) and good performance status. Many had progressed after prior local therapies and chemo-embolization
- Overall, sorafenib was well tolerated (Table Three). Both arms had similar rates of serious adverse events (SAEs). The most frequently reported grade three or four SAEs in the sorafenib compared to the placebo arms were diarrhea (8% versus 2%) and hand-foot skin reaction (8% versus <1%)
- Time to symptomatic progression (TTSP) as measured in this study was not different from placebo. The quality of life (QoL) endpoint warrants further study in this disease
- The survival advantage of 2.8 months is modest, but is in keeping with accepted progress seen in other refractory end-stage cancers with systemic agents. The median survival of 10.7 months is superior to any other median survival reported for advanced HCC in modern trials

Phase III Trials: Asia-Pacific Liver Cancer Trial

- The Asia-Pacific Liver Cancer Trial is a double-blind, randomized, placebo-controlled Phase III trial that has recently been completed
- 226 patients from China, Korea and Taiwan were enrolled and received either 400mg Sorafenib bid or placebo
- The results of this trial have not yet been published or presented. However, in August 2007 this trial was stopped early on the recommendation of the independent data monitoring committee after a planned review. This review demonstrated significantly improved overall survival, progression-free survival and time to progression in the sorafenib arm as compared to the placebo arm. Assuming this trial meets peer review standards, it is likely to lend further support for sorafenib in a more diverse HCC population

Conclusion

- Sorafenib, 400mg bid is the new standard for first-line treatment of advanced hepatocellular cancer
- While the benefits demonstrated to date are modest, it is the first agent to confer a survival benefit to patients with advanced HCC and validates the study of targeted agents in this challenging disease. The results to date support the use of sorafenib in similar patients to the SHARP trial

Future directions

- Assessment of sorafenib—in the adjuvant setting, after potentially curative treatments
  - after chemo-embolization
  - in patients with Child-Pugh B liver dysfunction
- Assessment of targeted agent combinations, to build on the benefit of sorafenib alone

Table Two. SHARP trial

	Sorafenib (n=299)	Placebo (n=303)	HR (95% CI)	*P-value*
Overall Response, n(%) CR PR SD PD	 0 7(2.3) 211(71) 54(18)	 0 2(0.7) 204(67) 73(24)		
TTP (months)	5.5	2.8	0.58 (0.44-0.74)	0.000007
TTSP (months)	NS	NS		0.77
OS (months)	10.7	7.9	0.69 (0.55-0.88)	0.00058

(CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; TTP: time to progression; TTSP: time to symptom progression; OS: overall survival; NS: non-significant)

Table Three. Adverse events

	Sorafenib		Placebo	
Drug-related AEs (%)	**All**	**Grade 3 / 4**	**All**	**Grade 3 / 4**
Diarrhea	39	8	11	2
Hand-foot skin reaction	21	8	3	<1
Weight Loss	9	2	<1	0
Pain	8	2	3	<1
Vomiting	5	1	3	<1
Alopecia	14	0	2	0
Anorexia	14	<1	3	<1
Nausea	11	<1	8	1
Liver dysfunction	<1	<1	0	0
Bleeding	7	<1	4	<1