Sorafenib for Advanced Hepatocellular Carcinoma

J. Knox, R. Cosby, K. Chan, and M. Sherman

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: February 14, 2008

This CED-SOS Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The report, which consists of the Recommendations and Evidentiary Base, is available on the CCO web site (http://www.cancercare.on.ca)

A CED-SOS Advice Report is a document developed by the PEBC in response to a request from the Committee to Evaluate Drugs (CED) for a review of the clinical evidence on a specific cancer drug or combination of drugs. An abbreviated systematic review of the literature is undertaken in a very short time period.

This particular document was developed by one clinical expert and one PEBC staff member. This document has been internally approved by PEBC management but has not been subject to a broader external review due to time constraints.

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Sorafenib for Advanced Hepatocellular Carcinoma: Recommendations and Evidentiary Base

J. Knox, R. Cosby, K. Chan, and M. Sherman

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The 2008 guideline recommendations were put in the Education and Information section. This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

QUESTION
What is the role of sorafenib (Nexavar) in adult patients with advanced hepatocellular carcinoma (HCC)? The outcomes of interest are survival, time to progression, tumour response, adverse effects, and quality of life.

TARGET POPULATION
The target population includes those that meet all of the following four criteria:

- Adult patients with advanced HCC, Child-Pugh Class A or B
- With or without previous surgery or locoregional treatments
- Who are no longer suitable for surgical or other curative approaches
- Who have either progressed on trans-arterial chemoembolization (TACE) or are not suitable for the TACE procedure

RECOMMENDATIONS
- Sorafenib can be administered to adult patients with advanced HCC who are Child-Pugh Class A and have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 for the purposes to prolong survival and improve time to progression.
• There is currently no evidence for or against the administration of sorafenib to adult patients with advanced HCC who are Child-Pugh Class B and have an ECOG Performance Status of 0-2. There is evidence for the safety of sorafenib in this group of patients, but efficacy has not yet been established.

KEY EVIDENCE

• The following three completed clinical trials involving sorafenib in advanced HCC comprise the evidence base and include one fully published Phase II trial (1), one Phase II RCT in abstract form (2), one Phase III RCT in abstract form (3).

  ➢ A North American Phase II study of sorafenib in advanced HCC (1) included both Child-Pugh A (72%) and B (28%) patients. In this study, 41.6% of all patients achieved partial response, minor response (25-50% tumour reduction), or stable disease (for at least 16 weeks). Independently assessed median time-to-progression (TTP) was 5.5 months and investigator-assessed median overall survival (OS) was 9.2 months. The most common grade 3 toxicities reported were fatigue (9.5%), diarrhea (8.0%), and hand-foot skin reaction (5.1%). No grade 4 toxicities were reported. In comparing Child-Pugh A (n=98) and B (n=38) patients, the pharmacological clearance of sorafenib as well as adverse events and dose intensity delivered were all very similar between the two groups. This trial, with evidence of efficacy and safety in advanced HCC, was the basis upon which the subsequent Phase III trial reported below was planned.

  ➢ A North American Phase II randomized trial of doxorubicin plus sorafenib (Dox + Sor) versus doxorubicin plus placebo (Dox + Pbo), in 96 Child-Pugh A patients, was conducted in North America and was published in abstract form and presented at the 2007 European CanCer Organization Conference (ECCO) (2). Median TTP was 8.6 months in the Dox + Sor arm and 4.8 months in the Dox + Pbo arm but did not reach statistical significance (p=0.076). However, OS was 13.7 months in the Dox + Sor arm compared to 6.5 months in the Dox + Pbo arm (p=0.0049). This corresponds to a hazard ratio (HR) of 0.45. Disease control rate (DCR=complete response [CR] + partial response [PR] + stable disease [SD]) was 81% in the Dox + Sor arm versus 57% in the Dox + Pbo arm. The most common grade 3-4 toxicities reported in the Dox + Sor versus Dox + Pbo arms were neutropenia (53% versus [vs] 46%) and fatigue (15% vs 15%). Although this trial is strongly positive in favour of the Dox + Sor arm, it requires further study to determine if the benefit was owing to a positive interaction in the Dox + Sor arm or to sorafenib alone.

  ➢ The Sorafenib HCC Assessment Randomized Protocol (SHARP) trial (3) was a large, international, double-blind, Phase III, multicentre, randomized trial comparing sorafenib (Sor) to placebo (Pbo) in Child-Pugh A patients. This trial was published in abstract form (Abstract LBA1) and presented at the 2007 annual meeting of the American Society of Clinical Oncology. In this trial, 602 patients (Sor, n=299; Pbo, n=303) were randomized. Those in the sorafenib arm received 400 mg orally twice daily (po bid) and those in the placebo arm received two tablets po bid. The HR for OS was 0.69 (95%CI, 0.55-0.88; p=0.00058). This corresponds to a 44% improvement in OS in favour of sorafenib. Median OS was 10.7 months in the sorafenib arm and 7.9 months in the placebo arm. The HR for TTP in the SHARP trial for sorafenib compared to placebo was 0.58 (95%CI, 0.44-0.74; p=7x10^-6). This corresponds to a 73% prolongation in TTP in patients treated with sorafenib. Median TTP was 5.5 months in the sorafenib arm compared to 2.8 months in the placebo arm. Time-to-symptomatic progression (TTSP) was not
significantly different in the two groups of patients (p=0.77). Response rate (CR + PR) was better in the sorafenib arm than the placebo arm, although not significantly so (2.3% vs 0.7%). Similarly, SD occurred more often in the sorafenib arm than the placebo arm, but the difference was not statistically significant (71 vs 67%). Both arms in SHARP had similar rates of serious adverse events (SAEs). The most frequently reported grade 3 or 4 SAEs in the sorafenib versus placebo arms were diarrhea (8 vs 2%) and hand-foot skin reaction (8 vs <1%). A subgroup analysis of different etiologies within the SHARP Trial data was recently conducted and presented. Specifically, patients with hepatitis C virus (HCV) demonstrated median OS in the Sor arm of 14.0 months versus 7.9 months in the Pbo arm (HR=0.58; 95%CI, 0.37-0.91). Median TTP among patients with HCV was 7.59 months in the Sor arm and 2.76 months in the Pbo arm (HR=0.44; 95%CI, 0.25-0.76).

QUALIFYING STATEMENTS

- In the SHARP trial (3), TTSP was measured using the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index 8 (FHSI-8), which is a tool designed to assess symptoms in hepatobiliary cancer patients in general but not designed specifically for HCC patients. The known group (discriminant) validity and concurrent convergent validity of this instrument were validated on just 51 patients, only 10 of whom had HCC (5). However, the minimal clinically important difference (MCID) for this tool has not been obviously established in the published literature, and the responsiveness (i.e., longitudinal validity) of this tool has not been established. Therefore, it remains unclear whether FHSI-8 can detect clinically important changes in the symptoms of patients with HCC over time. Furthermore, although TTSP was considered one of the two primary endpoints, the design of the study was not specifically powered for this endpoint. The lack of difference in the TTSP endpoint in the SHARP study may be the result of an insensitive measurement tool, lack of power for the TTSP endpoint, or a true absence of symptomatic benefit from sorafenib.

- The double-blind, randomized, placebo-controlled, Phase III Asia-Pacific Liver Cancer Trial was recently completed (6). The 226 patients from China, Korea, and Taiwan enrolled in this study received either 400 mg sorafenib bid or placebo. The primary outcomes were to compare OS, TTP, and progression-free survival (PFS) in the two arms. Because the results of this trial are not expected to be publically available until sometime in 2008, the data are not included in this report. However, in August 2007, this trial was stopped early on the recommendation of the independent data monitoring committee after a planned review of the data demonstrated significantly improved OS, PFS, and TTP in the sorafenib arm as compared to the placebo arm.

METHODS

This advice report, produced by the Program in Evidence-Based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the role of sorafenib for advanced hepatocellular carcinoma (HCC). For this project, the core methodology used to develop the evidentiary base was the systematic review. The body of evidence in this review is primarily comprised of Phase II and III randomized controlled data. The systematic review and the recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.
Literature Search Strategy

The MEDLINE (1950 through November [week two] 2007) and EMBASE (1980 through week 50 2007) databases were searched for relevant evidence. The American Society of Clinical Oncology (ASCO) Annual Conference Proceedings from 2000 through 2007 were searched, as were the ASCO Gastrointestinal (GI) Cancers Symposia Abstracts from 2004 through 2008 and the ECCO abstracts. The search terms used are shown in Table 1. The full MEDLINE and EMBASE literature search strategies can be found in Appendices A and B respectfully.

Relevant articles were selected and reviewed by one reviewer, and the reference lists from those sources were searched for additional trials.

Table 1. Literature search strategy.

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<th>Search date</th>
<th>Database</th>
<th>Search terms used</th>
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<td>December 18, 2007</td>
<td>MEDLINE</td>
<td>Liver carcinoma, Hepatocellular carcinoma, sorafenib,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nexavar, bay 43-9006</td>
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<tr>
<td>December 18, 2007</td>
<td>EMBASE</td>
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<tr>
<td>December 18, 2007</td>
<td>ASCO Annual Conference Proceedings</td>
<td>sorafenib, HCC</td>
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<tr>
<td>January 24, 2007</td>
<td>ECCO Conference Abstracts</td>
<td>sorafenib</td>
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<tr>
<td>January 28, 2007</td>
<td>ASCO GI Cancers Symposia Abstracts</td>
<td>sorafenib, HCC</td>
</tr>
</tbody>
</table>

Inclusion Criteria

Articles and abstracts were selected for inclusion in the systematic review if they were published English-language reports, involving human participants, of Phase II or III randomized controlled trials (RCTs) or cohort studies comparing sorafenib and another agent and/or placebo in patients with advanced HCC. Outcomes of interest were survival, time to progression, tumour response, adverse effects, and quality of life.

Exclusion Criteria

Letters, editorials, notes, retrospective studies, and non-systematic reviews were not eligible.

Synthesizing the Evidence

Due to the heterogeneity of the outcomes reported on, the varying designs of located studies, and the lack of fully published RCTs, data were not pooled using meta-analytic techniques.

CONFLICT OF INTEREST

One author (RC) of this report declared no potential conflict of interest related to the topic of this CED-SOS Advice Report. The other authors reported honoraria from Bayer HealthCare Pharmaceuticals of less than $1000 (KC), greater than $5000 over the past two years (JK), and greater than $5000 annually (MS).

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REFERENCES


Appendix A. MEDLINE search strategy.

1. exp Carcinoma/
2. exp Neoplasms/
3. 1 or 2
4. exp Liver/
5. hepat:.mp.
6. 4 or 5
7. 3 and 6
8. Liver Neoplasms/
9. Carcinoma, Hepatocellular/
10. (liver adj3 (cancer or carcinoma or tum: or neoplasm:)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11. (hepat: adj3 (cancer or carcinoma or tum: or neoplasm:)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. or/7-11
13. sorafenib.mp.
14. nexavar.mp.
15. bay 43-9006.mp.
16. or/13-15
17. 12 and 16
18. limit 17 to english language
Appendix B: EMBASE search strategy.

1. exp CARCINOMA/
2. exp NEOPLASM/
3. 1 or 2
4. exp LIVER/
5. hepat:.mp.
6. 4 or 5
7. 3 and 6
8. exp Liver Tumor/
9. Liver Cell Carcinoma/
10. (liver adj3 (cancer or carcinoma or tum: or neoplasm:)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
11. (hepat: adj3 (cancer or carcinoma or tum: or neoplasm:)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
12. or/7-11
13. SORAFENIB/
14. nexavar.mp.
15. bay 43-9006.mp.
16. or/13-15
17. 12 and 16
18. limit 17 to english language