Systemic therapy for hepatocellular carcinoma (HCC): from bench to bedside☆

Omar Abdel-Rahman ∗

Clinical Oncology Department, Ain Shams University, Egypt

Received 27 May 2013; accepted 13 August 2013
Available online 21 September 2013

KEYWORDS
Hepatocellular carcinoma; Systemic treatment

Abstract Primary liver cancer is the fifth most common cancer worldwide and the third most common cause of cancer mortality. For patients with early resectable disease, surgical resection or transplantation is considered a potentially curative modality for hepatocellular carcinoma (HCC); on the other hand, for patients with unresectable or metastatic disease, treatment is essentially palliative and prior to the approval of sorafenib, there was no globally approved systemic treatment for patients presenting with unresectable or metastatic HCC. Sorafenib is the only systemic treatment to demonstrate a statistically significant but modest overall survival benefit in a large phase III trial. Thus, novel systemic approaches represent a high unmet medical need in advanced HCC. In this review article, we will try to take a journey through the history of systemic therapeutic options for HCC passing through the current standard options and exploring the potential new systemic options for this disease.

© 2013 Production and hosting by Elsevier B.V. on behalf of National Cancer Institute, Cairo University.
Open access under CC BY-NC-ND license.
Introduction

Primary liver cancer is the fifth most common cancer worldwide and is the third most common cause of cancer mortality. Globally, over 560,000 people develop liver cancer each year and an almost equal number, 550,000, die of it. Liver cancer burden, however, is not evenly distributed throughout the world. Most HCC cases (>80%) occur in either sub-Saharan Africa or in Eastern Asia. China alone accounts for more than 50% of the world’s cases (age-standardized incidence rate (ASR) male: 35.2/100,000; female: 13.3/100,000) [1].

HCC is a complex disease associated with many risk factors and cofactors. In most patients, HCC is preceded by cirrhosis of the liver and, unsurprisingly, common causes of cirrhosis have been identified as key risk factors for HCC. Of particular importance is chronic infection with HBV or hepatitis C virus (HCV). Indeed, it has been estimated that HBV is responsible for 50-80% of HCC cases worldwide, whereas 10-25% of cases are thought to be a result of HCV infection [2].

At the initial diagnosis, surgical resection or transplantation is considered a potentially curative modality for HCC; Patients with localized resectable disease are usually treated with some form of localized therapy. Local therapeutic modalities include targeted therapy through hepatic artery combined with embolization, percutaneous ethanol ablation, radioembolization, radiofrequency ablation, and cryosurgery [3].

Prior to the approval of sorafenib, there was no globally approved systemic treatment for patients presenting with unresectable or advanced metastatic HCC. Sorafenib is the only systemic treatment to demonstrate a statistically significant but modest overall survival benefit in a large phase III randomized, placebo-controlled trial (SHARP; sorafenib HCC Assessment Randomized Protocol Trial) [4]. Thus, novel approaches for the treatment of unresectable advanced or metastatic HCC represents a high unmet medical need. In this review article, we will try to take a journey through the history of systemic therapeutic options for HCC passing through the current standard options and exploring the potential new systemic options for this disease.

Research methodology

An updated summary of the preclinical and clinical experience with various systemic therapies in HCC is presented in a chronological order. Data are based on abstracts from international conferences and journal articles found in a PubMed search of literature published up to June 2013.

Chemotherapy

Chemotherapeutic agents have been studied extensively in hepatocellular carcinoma (HCC), with phase II trials yielding response rates ranging from 10% to 20% but never demonstrating an improvement in overall survival compared with best supportive care. Doxorubicin is the most extensively studied agent in advanced HCC, with response rates ranging from 0% to 79% [5]. Other chemotherapy agents that have been studied in HCC include docetaxel, paclitaxel, irinotecan, capcitabine, tegafur-uracil (UFT) and gemcitabine; however, none of these agents has demonstrated any survival advantage [5-9].

Because of the lack of survival advantage with monotherapy for advanced HCC, combination regimens have been studied in HCC. Again, the results of combination chemotherapy regimens (gemcitabine-based, taxane based or anthracycline based) were disappointing with no demonstrated survival benefit [11-13]. Probably, the most interesting combination chemotherapy regimen is the PIAF regimen (cisplatin, interferon alfa-2b, doxorubicin, and 5-fluorouracil) which demonstrated a response rate of 26% and a median survival of approximately 9 months in a single-arm phase II trial [14]. These positive results led to the evaluation of PIAF in a large randomized study versus doxorubicin [15]. However, the results of this study was again disappointing and did not meet its primary endpoint, with median survivals of 8.6 months for PIAF versus 6.8 months for doxorubicin (P = 0.83) (Table 1).

Molecular targets in hepatocellular carcinoma

With the lack of a standard of care, the urgent need to evaluate novel therapeutic options for patients with advanced HCC became clear. These efforts began at the same period that basic science researchers were delineating a better profile of the carcinogenesis of HCC and the relevant pathways involved. Potential targets of interest in HCC include the epidermal growth factor receptors and the angiogenic pathway [16].
Epidermal growth factor receptor inhibitors

The importance of the epidermal growth factor receptors (EGFR) pathway in hepatocellular carcinoma (HCC) is still under investigation. Nonetheless, several EGFR tyrosine kinase inhibitors have been studied in HCC. Erlotinib has been studied alone and in combination in a number of phase II trials both as first line and after failure of sorafenib [17–19]; however the response rate was modest both in monotherapy and in combination.

Cetuximab, an anti-EGFR monoclonal antibody, was also tested in advanced HCC, both as a single agent and in combination, however it did not demonstrate significant antitumor efficacy worthy of further consideration in advanced HCC [20–22].

Inhibitors of the proangiogenic pathway

Angiogenesis, which involves the vascular endothelial growth factor (VEGF) family, is a critical component in the development of hepatocellular carcinoma (HCC). In preclinical studies, VEGF has been found to augment the metastatic potential of HCC tumors [23].

This metastatic potential is thought to be governed by the overexpression of platelet-derived growth factor receptor-beta (PDGFR-β) in HCC [29]. Sorafenib, a multi-tyrosine kinase inhibitor is the most extensively studied agent of this category.

Sorafenib preclinical pharmacology

Sorafenib, a multi-tyrosine kinase inhibitor, targets angiogenic VEGFR-1, -2, and -3; PDGFR-β; and tumorigenic RET, Flt-3, and c-Kit receptors. In human hepatocellular tumor cell lines, sorafenib potently inhibited cellular proliferations, Raf/MEK/ERK signaling and induced apoptosis [39].

Clinical experience with sorafenib

Clinical results in Phase I studies of sorafenib as a single agent were indicative of a therapeutic effect in HCC and led to the design of a single phase II trial of sorafenib in 137 patients with advanced-stage HCC yielding encouraging efficacy and tolerability results [40]. However, 33.6% of patients treated had stable disease (≥16 weeks) commensurate with an independently reviewed, relatively improved median time to progression of 5.5 months. The median overall survival of the study population was 9.2 months, comparing favorably with historical controls.

The results of this study provided the basis for the randomized, placebo-controlled Phase III study in subjects with advanced HCC Child–Pugh class A. This large (602 subjects) Phase III study was the first international, randomized, double-blind, placebo-controlled study to demonstrate a statistically significant and clinically meaningful improvement in OS in advanced HCC subjects treated with sorafenib over placebo. Of the 299 sorafenib subjects valid for ITT analysis, the median OS was 10.7 months in the sorafenib group and 7.9 months in the 303 subjects randomized to the placebo group. Therefore, sorafenib had a statistically significant effect on prolonging overall survival [42].
Another phase III randomised, double-blind, placebo-controlled trial was conducted in patients in the Asia-Pacific region with advanced hepatocellular carcinoma. Of these, 226 patients were randomly assigned to the sorafenib group (n = 150) or to the placebo group (n = 76). Median overall survival was 6.5 months in patients treated with sorafenib, compared with 4.2 months in those who received placebo [43]. Survival was 6.5 months in patients treated with sorafenib, compared with 4.2 months in those who received placebo [43]. And so, taken together with data from the Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP) trial, sorafenib seems to be an appropriate option for the treatment of advanced hepatocellular carcinoma.

### Sorafenib plus chemotherapy combination

In spite of improvement in terms of overall survival (OS) and time to progression (TTP), in all studies where sorafenib was compared to placebo, the sorafenib arm was not accompanied by a significant volumetric reduction, and this may explain the lack of any symptomatic improvement (time to symptomatic progression (TTSP) was almost identical between sorafenib and placebo).

Reviewing the chemotherapy outcome, although there is no convincing evidence in survival benefit to patients with advanced HCC, however true shrinkage (reduction in tumor size), has been consistently reported although the magnitude of response is lacking consistency.

This indicates the need for coupling sorafenib to a chemotherapeutic agent but:

- For patients with hepatocellular carcinoma, the toxicity profile of any chemotherapeutic agent of choice to be added to sorafenib should be taken into consideration
- The agent to be added to sorafenib should be effective in terms of Tumor Shrinkage & with minimal toxicity regarding: cardio-toxicity, HFSR, Diarrhea, Hepato-toxicity, bone marrow suppression (although not relevant to the toxicity profile of sorafenib, yet the HCC patients may have HCV related thrombocytopenia and variable degree of hypersplenism related pancytopenia), Circulatory Overload (Hypertension).

Accordingly, a number of phase 2/3 studies have been launched all over the world comparing “sorafenib plus” combination to sorafenib monotherapy; the first to these studies is the Nexavar-Tarceva Combination Therapy for First Line Treatment of Patients Diagnosed with Hepatocellular Carcinoma (SEARCH) (NCT00901901); initial results of the study were published in a press release in the ESMO congress 2012, Vienna and unfortunately it was negative with no improvement in overall survival or time to progression [41].

Our group in Egypt – the Egyptian Society of Liver Cancer – one study testing the value of combining Sorafenib Plus Tegafur-uracil (UFT) versus Sorafenib as First Line Systemic Treatment for Patients With Advanced Stage HCC (ESLC 1 study) (NCT01539018), the study is still recruiting participants; another German group has launched a phase 2 study testing the value of combining Sorafenib Plus Doxorubicin versus Sorafenib Alone for the Treatment of Advanced Hepatocellular Carcinoma (SORADOX study) (NCT01272557); this study is also recruiting participants; a 3rd group from the USA has launched a phase 2 study Combination of Temozolomide and Sorafenib in Advanced Hepatocellular Carcinoma, the study is still recruiting participants (NCT01687673).

### Other antiangiogenic therapies

Bevacizumab, an anti-VEGF monoclonal antibody, was also tested in advanced HCC, both as a single agent and in combination; however, despite initial encouraging results, further confirmatory studies were disappointing [25–29].

Cediranib, potent inhibitor of vascular endothelial growth factor signaling, has also been tested in a phase 2 study of advanced HCC, however, owing to toxicity, the drug was not found to be an appropriate treatment in patients with unresetable or metastatic HCC [30].

Sunitinib, another multi kinase inhibitor, although it had initial encouraging results both in the first line and post sorafenib settings [31–33], a phase 3 head to head comparison of sunitinib versus sorafenib showed discouraging results (NCT00699374).

Brivanib, a selective dual inhibitor of fibroblast growth factor and VEGF signaling, has demonstrated encouraging anti-tumor activity in preclinical and phase 1 and 2 studies (Table 2) [34]. However, despite positive signals seen with brivanib in the phase II study, the results of its phase III – reported in an abstract form earlier in 2012 – was negative (in this phase

---

### Table 2  Selected results of targeted agents used in HCC treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Dose</th>
<th>Disease control rate (%)</th>
<th>Median OS</th>
<th>Most common toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santoro et al. [10]</td>
<td>Trivatinib</td>
<td>360 mg twice daily</td>
<td>60</td>
<td>N/R</td>
<td>Neutropenia and anemia</td>
</tr>
<tr>
<td>Philip et al. [19]</td>
<td>Erlotinib</td>
<td>150 mg daily</td>
<td>59</td>
<td>13 ms</td>
<td>Skin toxicity and diarrhea</td>
</tr>
<tr>
<td>Zhu et al. [20]</td>
<td>Cetuximab</td>
<td>250 mg/m2</td>
<td>17</td>
<td>N/R</td>
<td>Elevated AST, hypomagnesemia, fever without neutropenia</td>
</tr>
<tr>
<td>Thomas et al. [28]</td>
<td>Bevacizumab/erlotinib</td>
<td>bevacizumab: 10 mg/kg every 14 days</td>
<td>62.5</td>
<td>13.5 ms</td>
<td>Hemorrhage, wound infection, thrombocytopenia and proteinuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>erlotinib: 150 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faivre et al. [33]</td>
<td>Sunitinib</td>
<td>50 mg/day for 4 weeks followed by 2 weeks rest</td>
<td>37.5</td>
<td>N/R</td>
<td>Thrombocytopenia, neutropenia and hand foot skin reaction</td>
</tr>
<tr>
<td>Park et al. [34]</td>
<td>Brivanib</td>
<td>800 mg once daily</td>
<td>48</td>
<td>10 ms</td>
<td>Fatigue, hypertension and diarrhea</td>
</tr>
</tbody>
</table>

*a N/R: not reported.*
3 study, brivanib did not significantly improve OS in advanced HCC patients who failed sorafenib) and further search for active second line agents is ongoing [35].

Thalidomide is another anti-neoplastic agent with anti-angiogenic and other mechanisms of action. Initial phase 1/2 data were encouraging with modest antitumor activity and tolerable side effects [36,37]; however, with the appearance of the results of phase 3 sorafenib studies, interest in thalidomide has faded away.

Linifanib is another potent and selective inhibitor of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinase families. In a phase II trial in patients with advanced HCC, Lin showed clinical activity objective response rate [ORR] 10.5% in Child-Pugh A patients [44]. So, it has been compared to sorafenib in a phase 3 study which showed that linifanib and sorafenib resulted in similar OS in advanced HCC. Predefined superiority and non-inferiority OS boundaries were not met for linifanib. Secondary endpoints (TTP and ORR) favored linifanib while safety results favored sorafenib[43].

mTOR inhibitors

Due to encouraging results in other solid tumors like kidney cancer and breast cancer, interest in mTOR inhibitors for HCC was stimulated recently, with a number of phase1/2 studies showing encouraging results [38]; however the issue of viral reactivation is alarming for the majority of HCC patients with underlying Hepatitis B or C infection.

C-Met inhibitors

A recent phase 2 study has provided hope for tivantinib (ARQ 197), a C-Met inhibitor, as a potential 2nd line candidate after sorafenib failure particularly in Met-high HCC; Time to progression was longer for patients treated with tivantinib (1.6 months) than placebo (1.4 months, \( p = 0.04 \)). For patients with MET-high tumours, median time to progression was longer with tivantinib than for those on placebo (2.7 months for 22 MET-high patients on tivantinib versus 1.4 months for 15 MET-high patients on placebo; \( p = 0.03 \)) (Table 2) [10]. This study provides a proof of concept that personalized targeted therapy is paving its way in the field of HCC research.

Immunotherapy for HCC

Another rapidly evolving and promising strategy is the use of immunotherapeutic approaches to treat HCC; the most commonly implemented immunotherapeutic strategy was the use of peptide vaccines. Based on the promising preclinical mice data, a number of phase 1 and 2 clinical studies have been conducted with initial encouraging results [45–47], however, data are still not mature enough in this research area to draw firm clinically oriented recommendations.

Conclusions

HCC is an active area for basic and clinical cancer research; with a rapidly changing therapeutic landscape (Fig. 1). We believe that basic and applied multicentre HCC research should be put as a priority for all the academic institutions in the Middle East to tackle this difficult to treat aggressive disease in the Middle East.

Source of support

None.

Conflict of interest

None.

References


Systemic treatment for (HCC): from bench to bedside


