Sorafenib and entecavir: The dioscuri of treatment for advanced hepatocellular carcinoma?

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Abstract
Hepatitis B virus (HBV) is responsible for 50%-80% of cases of hepatocellular carcinoma (HCC) worldwide. Entecavir (ET) is a potent inhibitor of chronic HBV-DNA polymerase, inhibiting both the priming and elongation steps of viral DNA replication. Sorafenib (SO) has proven efficacy in prolonging survival in patients with advanced HCC. In this frontier report we discuss a possible way to optimize treatment outcomes in patients with HBV and HCC by treatment with ET and SO, on the basis of our practice and published evidence from the literature.

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Key words: Entecavir; Hepatocellular carcinoma; Hepatitis B virus; Liver function; Sorafenib

INTRODUCTION
Over 350 million people globally are chronically infected with hepatitis B virus (HBV) and around 25% of these will develop hepatocellular carcinoma (HCC)

POTENTIAL ROLE OF ET AND SO
The most effective way to prevent HBV-related HCC is by vaccination but in patients already infected with HBV, antiviral therapy is the best strategy

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evaluated in both nucleoside-naive and lamivudine-resistant patients as well as being effective in both hepatitis B "e" antigen-positive and -negative nucleoside-naive patients. Antiviral therapy can reduce, but not eliminate the risk of HCC especially in patients with pre-existing cirrhosis and it is therefore important to maintain virological remission. The use of ET allows long-term HBV-DNA suppression with a low risk of resistance.

SO, a tyrosine kinase inhibitor, has been demonstrated in two large scale randomized, double-blind, placebo-controlled, multicentre, phase III trials (the SHARP trial and the Asia-Pacific trial) to prolong median overall survival and delay the median time to progression in patients with advanced HCC[12,13]. The SHARP study was the first to show an overall survival benefit for SO in patients with advanced HCC, in which the overall survival was 10.7 mo[14]. Subanalyses of the SHARP population based on a range of parameters including aetiology (hepatitis B virus present/absent); tumour burden (macroscopic vascular invasion and/or extrahepatic spread present/absent); presence or absence of either lung or lymph node metastasis at baseline, confirmed the efficacy and safety of SO in these subpopulations indicating that SO is effective for patients from the AP region with advanced HCC, irrespective of baseline status[15,16].

Individually ET and SO have been demonstrated to have important roles in the management of patients with HBV and HCC but how best should we use these agents - in combination or as a sequential strategy. The problem is that although there are a number of published guidelines on the treatment of patients with HBV there are no precise indications on the use of antiviral agents in patients with HBV-related HCC, however it is recognized that the goal of antiviral therapy for HBV is to preserve liver function and prevent the development of cirrhosis and HCC. Early intervention is therefore necessary to prevent liver cell damage and decrease viral genome integration. We believe that it is vital to prevent the deterioration of liver function as modulation of liver function may affect survival directly and indirectly but also it may have an impact on the patient's ability to tolerate subsequent treatments.

In a study by Jin et al[17], first-line ET monotherapy was effective in HBV patients (with and without HCC), improved hepatic function and importantly was associated with increased survival after eradication of HCC - confirming previous results that it improved liver function in patients with decompensated cirrhosis[18,19]. Considering that liver function is a key factor in deciding treatment options for a given patient and concomitant liver dysfunction often hampers both curative and palliative therapies, the fact that ET can improve hepatic function is decisive in the clinical scenario[20]. Furthermore, in a study by Chang et al[21] the majority of nucleoside-naive patients with HBV who were treated with long-term ET achieved substantial histological improvement together with regression of fibrosis or cirrhosis. SO has also shown promising antifibrotic activity with efficacy at relatively low doses at the early stage of liver fibrosis[22].

**OUR EXPERIENCE**

In our unit, we treated a total of 15 patients (1 male; aged 62-76, median 67 years) with advanced HCC and a history of HBV cirrhosis from October 2008 to December 2011. Diagnosis of advanced HCC was made according to the Barcelona Criteria using contrast enhanced ultrasound, elevated values of alpha-fetoprotein and/or liver biopsy. Ten patients had intermediate BCLC stage B and 5 had advanced BCLC stage C and all had Child Pugh A (9 with an A6, 6 with A5). The baseline characteristics of patients are summarized in Table 1.

All patients achieved a complete clearance of HBV-DNA following the administration of ET (0.5 mg/d) before the initiation of SO. The dosage of SO was gradually increased over a 6-wk period to reach the recommended dosage of 800 mg/d.

The median survival in these patients with HCC and HBV was 26.5 mo (range 10-36 mo). No patient stopped therapy due to AEs (cardiac, gastrointestinal, haematological, neurological or dermatological, or endocrinological). All patients had blood pressure within the accepted recommend range, assumed regular cardiac medication or intervention of sorafenib therapy due to adverse events.

**Table 1 Baseline characteristics and main treatment outcomes of our cohort (n = 15) n (%)**

| Characteristic                              | Value          |
|--------------------------------------------|----------------|
| Male                                       | 1 (6.7)        |
| Age, yr (range)                            | 67 (62-76)     |
| BCLC stage                                 |                |
| B - intermediate                            | 10 (66.7)      |
| C - advanced                               | 5 (33.3)       |
| Child-Pugh score                           |                |
| 5                                          | 6 (40)         |
| 6                                          | 9 (60)         |
| Treatment outcomes                         |                |
| Overall survival, mo (range)               | 26.5 (10-36)   |
| Liver decompensation                       | 4 (26.7)       |
| Hepatocellular carcinoma progression       | 3 (20.0)       |

All subjects achieved viral clearance following entecavir treatment before the initiation of sorafenib 800 mg/d.
allow to retrieve any definite cause-effect relationship.

These limitations taken into account, these results are somehow encouraging: this may be, at least in part, due to the viral clearance achieved by patients. We cannot rule out, however, that the longer survival observed in our patients can be attributed to the high proportion of subject with BCLC-B stage HCC.

CONCLUSION

On the basis of our experience and current literature, therefore, we propose that in patients with HBV monotherapy with ET should be given initially to reduce viral load and preserve liver function thereby allowing follow-up treatment with SO to treat HCC. We believe that this treatment approach may represent a potential improvement in the current management of advanced HCC in patients with concomitant HBV infection. However, further, well-designed studies are needed to investigate the efficacy and safety of this therapy in a large sample of patients. If such study will provide positive results, we feel that SO and ET will be considered the “Dioscuri”, the warrior twins of the Greek mythology, of the treatment of advanced HCC.

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