Introduction

Sorafenib is currently the standard systemic therapy approved for treatment of hepatocellular carcinoma (HCC) in patients with well-preserved liver function (Child-Pugh class A), advanced-stage HCC (Barcelona Clinic Liver Cancer-C), and progressive HCC after locoregional therapy [1–4]. Treatment with sorafenib is recommended based on its efficacy and safety, as reported by two international randomized controlled trials: the SHARP (Sorafenib HCC Assessment Randomized Protocol) and the Asia-Pacific trials [5, 6]. In addition, the efficacy and safety of the drug in clinical practice have been addressed by several field-practice experiences, including the multinational GIDEON (Global Investigation of therapeutic DEcisions in HCC and Of its treatment with...
sorafenib (sora) study [7]. In Japan, sorafenib has been administered in accordance with the consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology [8]. Sorafenib is also recommended in cases with Child-Pugh class A where transcatheter arterial chemoembolization (TACE) [9] and hepatic arterial infusion chemotherapy (HAIC) are not indicated.

Recently, several case reports [10, 11] and a nationwide survey [12] have been published in which a complete response (CR) was obtained following sorafenib treatment. However, such cases are rare, and most long-term survivors following sorafenib treatment belong to the non-CR group and obtain a partial response (PR) or stable disease (SD). However, little data are available regarding long-term survivors following sorafenib treatment for advanced HCC. To address this issue, we held a workshop at the 50th annual meeting of the Liver Cancer Study Group of Japan, which took place from June 5 to 6, 2014 in Kyoto (congress president: Prof. Masatoshi Kudo). In this review, we present an overview of the factors influencing the management of long-term survivors following sorafenib treatment in Japan and discuss the potentially confounding effects associated with each factor as well as the possible interactions between the factors.

**Summary of Presentations from Eight Institutions**

The profiles of the long-term (>3 years) survivors following sorafenib treatment from eight institutions are shown in Table 1. At the beginning of the workshop, Imura and colleagues (Department of Surgery, The University of Tokushima) presented a case of a 50-year-old man who developed a very large HCC with intrahepatic metastases in the right lobe of the liver (fig. 1a–c). He was administered sorafenib, and a subsequent treatment assessment revealed a PR (fig. 1d–f). Right hepatectomy as a conversion surgery was performed, and FGF4 gene amplification was detected in the resected specimen [13]. This patient has remained alive with no sign of recurrence for 1.5 years following right hepatectomy. Imura and colleagues also presented 4 additional patients with HCC showing long-term survival after sorafenib treatment; 3 of these 4 patients underwent conversion/salvage treatment (locoregional therapy in 2 patients and surgical resection in 1 patient). All these patients have remained alive, and sorafenib therapy is ongoing for 2 patients.

Takeyama and colleagues (Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University) presented 5 cases of HCC showing long-term survival after sorafenib treatment. Nishijima and colleagues (Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital) presented 5 cases of HCC showing long-term survival after sorafenib treatment. Morimoto and colleagues (Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine) presented 5 cases of HCC showing long-term survival after sorafenib treatment. Hattori and colleagues (Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital) presented 5 cases of HCC showing long-term survival after sorafenib treatment.

<table>
<thead>
<tr>
<th>Presenting group</th>
<th>Patients, n</th>
<th>Long-term survivors (male/female)</th>
<th>Etiology B/C/NBNC</th>
<th>TNM stage 3/4A/4B</th>
<th>Treatment response CR/PR/SD/PD</th>
<th>Conversion/salvage options (No. of patients)</th>
<th>Long-term survival-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imura1</td>
<td>–</td>
<td>4 (2/2)</td>
<td>4/0/0</td>
<td>–/–/3</td>
<td>Surgery (1), RFA</td>
<td></td>
<td>Conversion surgery</td>
</tr>
<tr>
<td>Takeyama2</td>
<td>–</td>
<td>5 (5/0)</td>
<td>0/3/2</td>
<td>0/1/4</td>
<td>Surgery (3), TACE, RFA</td>
<td></td>
<td>Downstaging Multidisciplinary treatment</td>
</tr>
<tr>
<td>Wada3</td>
<td>131</td>
<td>9 (7/2)</td>
<td>–</td>
<td>–/–/3</td>
<td>2/1/6/0</td>
<td>Systemic chemotherapy (5), TACE (4)</td>
<td>Especially long SD Good liver function</td>
</tr>
<tr>
<td>Urata4</td>
<td>60</td>
<td>3 (2/1)</td>
<td>–</td>
<td>0/1/0</td>
<td>Combined with TACE (2)</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Hattori5</td>
<td>147</td>
<td>7 (5/2)</td>
<td>2/3/2</td>
<td>–/–/3</td>
<td>2/1/4/0</td>
<td>Surgery (1), RFA (2), radiation (4)</td>
<td>VEGF/AFP response Multidisciplinary treatment</td>
</tr>
<tr>
<td>Morimoto6</td>
<td>337</td>
<td>15 (14/1)</td>
<td>0/5/5</td>
<td>2/2/6</td>
<td>3/4/4/4</td>
<td>TACE, RFA</td>
<td>Long PPS Good liver function</td>
</tr>
<tr>
<td>Ueshima7</td>
<td>222</td>
<td>15 (9/6)</td>
<td>6/6/3</td>
<td>9/1/5</td>
<td>4/5/6/0</td>
<td>Surgery (1), TACE, RFA, HAIC</td>
<td>Salvage options Good liver function</td>
</tr>
<tr>
<td>Nishijima8</td>
<td>465</td>
<td>12 (9/3)</td>
<td>3/4/5</td>
<td>6/0/6</td>
<td>2/3/7/0</td>
<td>TACE (3), chemotherapy (1)</td>
<td>Good liver function Low DCP, disease control</td>
</tr>
</tbody>
</table>

**TNM** = Tumor-node-metastasis; **B/C/NBNC** = HBV-positive/HCV-positive/negative for HBV and HCV, the so-called ‘non-B non-C’.

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ing long-term survival following sorafenib treatment. Of these, 3 patients underwent salvage hepatectomy with or without radiofrequency ablation (RFA) [14]. Furthermore, additional locoregional treatment (TACE or RFA) was carried out while sorafenib treatment continued. This group suggested that multidisciplinary treatment, including surgical treatment, might improve survival following sorafenib administration.

Wada and colleagues (Department of Hepato-Biliary-Pancreatic Surgery, National Hospital Organization, Kyushu Medical Center) presented 9 cases of long-term survivors (6.9%) out of 131 patients with HCC who started treatment with sorafenib monotherapy (mainly half-dose sorafenib) between 2009 and 2013. Of these, 2 patients achieved a CR, 1 had a PR, and the remaining 6 patients had SD. Sorafenib therapy exceeding 3 years of duration was administered only to 1 patient who achieved an especially long SD. Of the remaining 8 patients, 7 underwent post-sorafenib options, including systemic chemotherapy (n = 5) and/or TACE (n = 4).

Urata and colleagues (Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine) presented 7 cases of long-term survivors (5.0%) out of 60 patients treated with sorafenib for HCC. Two of the 3 long-term survivors received TACE combined with sorafenib.

Hattori and colleagues (Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital) presented 7 cases of long-term survivors (4.8%) out of 147 patients with HCC who started sorafenib monotherapy between July 2009 and November 2013. Two patients initially received full-dose sorafenib, and the remaining 5 received a half-dose regimen. The median duration of sorafenib therapy was 980 days. Of these 7 patients, 2 achieved a CR, 1 had a PR, and the remaining 4 had SD. All of these long-term survivors underwent multidisci-

**Fig. 1.** A 50-year-old man with a very large HCC achieved a PR following sorafenib administration. **a–c** Computed tomography scan performed before sorafenib treatment showing a huge HCC with intrahepatic metastases in the right lobe. **a** Arterial phase. **b** Portal phase. **c** Delayed phase. **d–f** Following sorafenib treatment, the main tumor had shrunk and some of the intrahepatic metastases disappeared. **d** Arterial phase. **e** Portal phase. **f** Delayed phase.
plinary treatment including conversion surgery (n = 1), RFA (n = 2), or radiation therapy (n = 4). Furthermore, Hattori and colleagues reported that a decreased plasma vascular endothelial growth factor (VEGF) concentration, 8 weeks after starting sorafenib treatment, may predict survival in patients with advanced HCC [15]. In univariate analysis, a decrease in VEGF and an early alpha-fetoprotein (AFP) response were significantly associated with survival following sorafenib treatment. All 4 patients who showed a decrease in VEGF and an objective response (CR or PR) survived during the observation period.

Morimoto and colleagues (Department of Hepatobiliary and Pancreatic Medical Oncology, Kanagawa Cancer Center) presented a multicenter study from the Kanagawa Liver Study Group, detailing the cases of 15 long-term survivors (4.5%) out of 337 patients with HCC who started treatment with sorafenib monotherapy between July 2009 and December 2013. The median duration of progression-free survival of the long-term survivors following sorafenib therapy was 12.7 months, and a significantly longer post-progression survival (PPS) was associated with the use of post-sorafenib salvage options. Good pretreatment liver function and low baseline levels of AFP and des-γ-carboxy prothrombin (DCP) were associated with longer survival. Furthermore, this group indicated that initial treatment with half-dose sorafenib led to fewer severe adverse events and a comparable survival benefit compared to the use of full-dose sorafenib in select patients with HCC, particularly those of advanced age [16].

Ueshima and colleagues (Department of Gastroenterology and Hepatology, Kinki University School of Medicine) presented the cases of 12 long-term survivors (6.8%) out of 222 patients with HCC who started sorafenib monotherapy between May 2009 and December 2013. Of these 15 long-term survivors, 9 patients were tumor-node-metastasis stage 3 (according to the Liver Cancer Study Group of Japan staging criteria), 1 patient was stage 4A, and 5 were stage 4B. Four patients achieved a CR, 5 had a PR, and the remaining 6 had SD. The 3 patients who achieved a CR have remained alive with or without sorafenib continuation [17], and a patient who achieved PR underwent conversion surgery with no sign of recurrence since the surgery. Of the remaining 10 patients who achieved a PR or SD, 6 patients underwent post-sorafenib salvage treatment (TACE, HAIC, or clinical trials), and 4 patients underwent additional locoregional therapy with sorafenib continuation.

Nishijima and colleagues (Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital) presented an overview of long-term (>3 years) survival following sorafenib treatment was collated from eight Japanese institutions. A total of 70 cases of long-term survival following sorafenib treatment were presented and the long-term survival rate at each institution ranged from 2.6 to 6.9% (mean, 4.5). Clinically, sorafenib is characterized by a low objective tumor response rate but a relatively high disease control rate (2% PR rate and 40% SD rate) [5, 6]. Our expert panel demonstrated that, among 58 long-term survivors at five institutions, 13 patients achieved a CR (22.4%), 14 had a PR (24.1%), 27 had a SD (46.5%), and the remaining 4 had progressive disease (PD) (table 1). This shows that obtaining an objective response is of primary importance to long-term survival following sorafenib administration. Sorafenib monotherapy exceeding a 3-year duration is rare, and most of the patients receiving sorafenib require other treatment modalities in the form of a multidisciplinary therapy. Imura and colleagues emphasized conversion surgery for HCC that has been downstaged in patients who achieve PR. Takeyama and colleagues and Hattori and colleagues emphasized the use of salvage options for recurrent HCC during sorafenib treatment. Wada and colleagues, Morimoto and colleagues, and Ueshima and colleagues highlighted the importance of a continuation of sorafenib for as long as possible, and the latter two groups further reported the utility of post-sorafenib options to prolong PPS. Furthermore, good pretreatment liver function and low baseline levels of AFP and DCP have been reported as predictors of favorable long-term survival. Based on these reports, we categorized long-term survival-related factors as follows: (1) conversion options, including hepatic resection after successful sorafenib treatment, (2) additional salvage options with sorafenib continuation when PD is confirmed,
(3) long-term sorafenib treatment, (4) effective post-
sorafenib options to prolong PPS, and (5) good pretreat-
ment liver function. These categories appear to reflect the
actual patterns of management in practice for long-term
survivors following sorafenib treatment in Japan.

Sorafenib has been established as a standard therapy to
prolong survival in patients with advanced HCC, but it
provides only a small treatment response. A recent na-
tionwide survey to examine the clinical characteristics of
patients who obtained a CR following sorafenib use
showed that only 18 patients (0.6%) obtained a CR out of
3,047 patients who were treated with sorafenib [12]. Pred-
ictive factors in the CR group were female sex, low body
weight (<59 kg), early clinical stage, and small initial dose
of sorafenib, implying that it is difficult to predict re-
sponders using baseline clinical characteristics of pa-
tients. Biomarkers that are able to predict patient progno-
sis or response to therapy may represent a major advance-
tment towards a more personalized, tailored treatment for
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tment towards a more personalized, tailored treatment for
cancer patients [19, 20]. Arao et al. [13] reported that
FGF3/FGP4 gene amplification is frequently observed in
tumors that respond to sorafenib. However, this amplifi-
cation was only observed in around 2% of HCCs. HCC is
a highly heterogeneous disease, and the identification of
biomarkers is complex and has been poorly explored thus
far. Llovet et al. [21] studied plasma biomarkers as predic-
tors of outcome in patients with advanced HCC. They
measured baseline levels of plasma biomarkers in 491 pa-
tients, and again after 12 weeks in 305 patients participat-
ing in a phase III randomized controlled trial (SHARP
trial). They concluded that angiopoietin-2 and VEGF
were independent predictors of survival in patients with
advanced HCC, and that none of the biomarkers tested
significantly predicted response to sorafenib.

With regard to on-treatment biomarkers, assessments
of early AFP response [22] and a paradoxical increase in
DCP [23] have been reported. Personeni et al. [24] have
investigated the prognostic utility of serum AFP response,
defined as a >20% decrease in AFP levels during 8 weeks
of treatment with sorafenib, and concluded that the as-
seSSment of AFP response may be considered as an alter-
native to RECIST for monitoring sorafenib response in
HCC. In the workshop, Hattori and colleagues reported
on the utility of measuring decreases in VEGF, in addi-
tion to the assessment of AFP response. They reported
that all patients who had both a VEGF decrease and an
AFP response survived during the observation period
(median, 19.7 months), and the triple combination of
plasma VEGF decrease, AFP response, and modified RE-
CIST is associated with an extremely favorable prognosis
[15]. On-treatment biomarkers are important to identify
patients who can expect long-term survival following
sorafenib therapy, although their radiologic findings may
not be categorized as objective responses.

To obtain a favorable outcome for HCC patients when
locoregional therapy [9, 25] is not indicated, patients
should immediately be treated with sorafenib, and should
continue to be treated with the drug for as long as possi-
ble. If necessary, additional salvage options during
sorafenib treatment or post-sorafenib therapy, such as
second-line targeted therapy, may prolong survival. Al-
though further research to optimize the use of sorafenib
is ongoing, in particular to investigate potential labora-
tory and/or genetic biomarkers of response, the present
consensus seems to accurately reflect the patterns of man-
agement of HCC currently practiced in Japan and also
provides valuable information for other countries.

Disclosure Statement

The authors declare that no financial or other conflicts of inter-
est exist in relation to the content of this article.

References


