Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment

Masatoshi Kudo\textsuperscript{a} Franco Trevisan\textsuperscript{b} Ghassan K. Abou-Alfa\textsuperscript{c,d}
Lorenza Rimassa\textsuperscript{e}

\textsuperscript{a}Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan, \textsuperscript{b}Semeiotic Unit, Department of Medical and Surgical Sciences, Alma Mater Studiorum – University of Bologna, Bologna, Italy, \textsuperscript{c}Memorial Sloan Kettering Cancer Center, \textsuperscript{d}Weill Cornell Medical College, N.Y., USA, \textsuperscript{e}Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, Milan, Italy

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Abstract
Western and Eastern perspectives on therapeutic guidelines for hepatocellular carcinoma (HCC) have many commonalities but may also differ in certain aspects, as described in this article. In view of the limited therapeutic options for advanced HCC, evidence-based therapies are few, and thus there is a dependence on consensus-based guidelines. This article focuses on the Italian Association for the Study of the Liver guidelines and the Japanese approaches to therapy, while drawing attention to certain controversies from other academic bodies where applicable and appropriate.

Therapeutic Guidelines: The Western Perspective

In recent years several Western scientific associations have released and/or updated guidelines for the management of hepatocellular carcinoma (HCC) \cite{1–3}. Refinements based on updated evidence and actual clinical practice have also been proposed \cite{4}. The key points of Western guidelines are:

1. **Surveillance.** Six-monthly liver ultrasound examinations should be performed by experienced personnel. The measurement of alpha-fetoprotein combined with ultrasound is not
indicated because it barely (6–8%) increases the sensitivity, but significantly reduces the cost-effectiveness of surveillance. The target group comprises Child A/B cirrhotic patients, Child C patients listed for transplantation, non-cirrhotic hepatitis B surface antigen (HbsAg) carriers with active disease (or a family history of HCC), and hepatitis C virus (HCV)-infected patients with advanced fibrosis. There are different opinions regarding the use of alpha-fetoprotein, and the guidelines still lack recommendations or are unclear with respect to patients with non-alcoholic fatty liver disease, the population that has experienced the highest increase in HCC incidence in the Western Hemisphere.

2. Diagnosis. When a new nodule is detected by ultrasound in a cirrhotic liver, the recall policy is driven by the nodule size: for nodules <1 cm, 3-monthly ultrasound surveillance is recommended; for nodules >1 cm, HCC diagnosis requires detection of the typical vascular hallmarks (wash-in in the arterial phase and wash-out in the portal/delayed phases) by one radiological technique (computed tomography [CT] or magnetic resonance imaging [MRI]) at specialist centers [1–3] or by two radiological techniques at non-specialist centers [2]. The Italian Association for the Study of the Liver (AISF) also includes contrast-enhanced ultrasound among the diagnostic tools that are able to characterize nodules [4]. A “panoramic” imaging technique (CT or MRI) remains mandatory to assess the global tumoral burden for all guidelines. MRI has the highest sensitivity for detecting the typical vascular pattern in HCC <2 cm and is superior for the detection of hypovascular HCC when hepatocyte-specific contrast agents and post-vascular phase assessments are used. A biopsy is required if atypical features are evident on imaging and in noncirrhotic patients. A negative biopsy does not rule out malignancy, and 3-monthly ultrasound examinations are recommended. It is important to note that these diagnostic guidelines and tools are limited in scope to the screening population described herein.

3. Staging. All Western hepatology guidelines have endorsed the Balcelona Clinic Liver Cancer (BCLC) staging system for classification of patients into five prognostic strata according to their cancer burden, liver function, and performance status (PS). This system also proposes, in an evidence-based way, the standard of care treatment for each stage. However, because PS 1 does not preclude access to any available treatments for HCC, the Italian AISF has modified the BCLC therapeutic algorithm, and does not consider PS 1 a condition per se sufficient to up-grade a patient from earlier stages to advanced stages, for which only systemic therapy with sorafenib is recommended (AISF-BCLC staging system). Oncology experts differ in their opinions regarding the BCLC staging system, and some of them favor more precise systems [e.g., the Cancer of the Liver Italian Program, among others] for assessing advanced disease [5].

4. Treatment. Despite the BCLC indications, most associations (including AISF) have endorsed a more patient-tailored approach that is based on the multidisciplinary evaluation of each case and includes alternative first-line options [4]. Some key recommendations are (a) the presence of portal hypertension, hyperbilirubinemia, and multinodularity do not preclude hepatic resection, although this option must be accurately weighed against the risk of post-operative decompensation; (b) according to “transplant benefit” policy, liver transplantation may be considered even in patients slightly exceeding the Milan criteria as part of “expanded criteria” or “down-staging” protocols; (c) transarterial chemoembolization (TACE) should be adopted as the first-line therapy for intermediate (BCLC stage B) patients if they are not amenable to curative treatments (surgery or ablation); (d) the presence of segmental portal invasion is not a contraindication to TACE, although systemic therapy has shown possible benefits for these patients as a part of controlled studies; (e) the absence of an objective (complete or partial) response in treated lesions after two courses of TACE is considered a treatment failure, and sorafenib should be started (fig. 1); (f) combined loco-regional therapies (TACE plus ablation) offer maximum flexibility, allowing a nodule-by-nodule tailored...
approach. Therefore, in non-surgical cases, a combined/sequential treatment should be considered for multinodular disease treated with TACE and for nodules >3 cm undergoing ablation. It is important to note that other guidelines, e.g., those of the National Comprehensive Cancer Network, are more cautious in these regards: they continue to limit transplantation to patients meeting published criteria and refrain from recommending combined local and systemic therapies, citing a lack of supporting data.

**Therapeutic Guidelines: The Eastern Perspective**

1. **Evidence-Based Treatment Algorithm**

   The original Japan Society of Hepatology (JSH) HCC guidelines and all later updates contain an evidence-based treatment algorithm that is simple and easy to memorize. The algorithm includes three factors: (i) the degree of liver damage, (ii) the number of tumors, and (iii) the tumor diameter (fig. 2). The recommended treatment options can be narrowed down...
to one or two by referring to this algorithm. The most recent version of the evidence-based treatment algorithm can be summarized as follows:

1. The order of the recommendations for surgical resection and percutaneous radiofrequency ablation (RFA) has been clarified. Based on the results of large nationwide cohort studies conducted by the Liver Cancer Study Group of Japan (LCSGJ) [6, 7], surgical resection is set as the first therapeutic choice for HCC patients with a single tumor with liver damage of grade A or B. If the tumor is smaller than 3 cm in cases meeting the above conditions, RFA is recommended as the second choice. During the target period for the current revision (2007–2011), there were three randomized controlled trials (RCTs) comparing surgery and RFA [8–10]. However, the results of these RCTs were not reflected in the treatment algorithm because the trials had several problems, as described elsewhere [11]. For a patient with liver damage of grade A or B and two or three tumors smaller than 3 cm, either surgical resection or RFA is recommended with no priority, based on a Japanese cohort study [6, 7].

2. Based on the results of the phase III clinical trial of sorafenib versus placebo in patients with advanced HCC (the SHARP study) [12], the multi-tyrosine kinase inhibitor sorafenib is suggested in the third version of the treatment algorithm. In patients with liver damage of grade A or B and four or more tumors confined to the liver, systemic chemotherapy, including molecular-targeted agents and hepatic arterial infusion chemotherapy (HAIC), is the second recommended treatment after TACE.

3. Since the first JSH-HCC guidelines, the assessment of liver damage covered five factors, including the indocyanine green (ICG) test, and has been used as an indicator of liver func-
tion. Although the ICG test is considered indispensable for surgical decision making in Japan, it is not routinely performed before non-surgical treatments such as RFA and TACE in current daily practice in Japan. The Child–Pugh classification serves as a substitute liver function grading system only before non-surgical treatments.

2. Consensus-Based Treatment Algorithm

Although sorafenib is recommended for patients with segmental portal vein invasion or portal invasion at the first portal branch (Vp1–3), the JSH-LCSGJ algorithm reflects the consensus that it is not recommended for patients with portal invasion at the main portal branch (Vp4) because of the risk of hepatic failure. However, HAIC is still recommended for patients with Vp4, and therefore recommendations regarding HAIC were left unchanged [13]. Moreover, because locoregional therapy for Child–Pugh C patients is now widely used, and many studies have reported its survival benefits, it is now described as a "well accepted treatment" rather than an "experimental treatment" in the revised algorithm (fig. 3) [14].

3. Definition of TACE Failure/Refractoriness

In the 2010 version of the JSH consensus-based treatment algorithm [15], TACE failure/refractoriness was defined assuming the use of superselective lipiodol TACE—which has been widely used worldwide, and particularly in Japan—and areas with lipiodol deposition were considered to be necrotic. However, this concept is not well accepted internationally [16]. Furthermore, following the approval in Japan in February 2014 of embolic drug-eluting beads (DEBs) that do not use lipiodol, the phrase needed to be changed from "lipiodol deposition" to "necrotic lesion or viable lesion." Accordingly, the section was revised to define TACE failure as an ineffective response after two or more consecutive TACE procedures as evaluated by CT or MRI after 1–3 months, even after chemotherapeutic agents have been changed and/or the feeding artery reanalyzed. Moreover, the appearance of new lesions in the liver in addition to those lesions recorded at the previous TACE procedure (other than the nodule being treated) was added to the definition of TACE failure/refractoriness. Following discussion of other issues related to continuous elevation of tumor markers, vascular invasion, and extrahepatic spread, descriptions similar to those in the previous version were approved (table 1). The revisions to these TACE failure definitions were approved by more than 85% of HCC experts.

Controversies Regarding Medical Treatment

The advent of sorafenib as a standard of care for advanced HCC [12] settled the basic question of how to treat that condition, but raised many other questions, the most contemporary of which concern the use of sorafenib in more cirrhotic settings and the influence, if any, of the etiology of HCC on outcomes.

Sorafenib was first approved by the United States Food and Drug Administration without any reference to the degree of cirrhosis [17] because of the "paucity of treatment options and variability in CP Scoring" [18]. In the phase II trial evaluating sorafenib in patients with advanced HCC, of 137 patients, 38 had Child–Pugh B cirrhosis [19]. In a retrospective analysis, it was found that the median duration of therapy was 4 months for Child–Pugh A patients and 1.8 months for Child–Pugh B patients, with a median overall survival (OS) of 9.5 months versus 3.2 months, respectively [20]. However, the fact that similar pharmacokinetics were evident in the two groups adds to the controversy. On the other hand, a phase I study evaluating sorafenib in 150 patients with organ dysfunction (including 17 patients with HCC) indicated that treatment with sorafenib was associated with dose-limiting elevations in serum biliru-
bin concentration in patients with more advanced Child–Pugh scores [21]. Based on these observations, the authors recommended a dosing schedule for sorafenib based on bilirubin
levels. This concept remains controversial, with a post-marketing study showing similar overall safety profiles and dosing strategies in the different Child–Pugh groups [22].

Multiple studies have shown that patients with Hepatitis B Virus (HBV)-related HCC who were treated with sorafenib had a modest prolongation in median OS in contrast to HCV-related HCC patients who had a substantial improvement in survival almost double that of the former group [23–25]. Within the limitations of the retrospective nature of most of these data, an etiology-dependent genomic difference in HCC was theorized. CTNNB1 mutations are more commonly observed in HCV-related HCC than in HBV-related HCC and are associated with a specific WNT gene expression profile [26]. Sorafenib has been shown to interfere with WNT signaling output, leading to HCC growth suppression in preclinical models. Another explanation is the induction of sorafenib target CRAF by HCV core protein [27]. Although more exploration is certainly required, it should be emphasized that the utility of sorafenib is not undermined by this observation, and sorafenib remains an effective and life-prolonging therapy for HCC, irrespective of etiologic factors. Nonetheless the advent of next-generation sequencing of the somatic mutations in HCC will add to the controversy and may guide the next wave of clinical trials as the genetic heterogeneity and complexity of HCC become more evident and increasingly recognized.

**Is It Time for a Second-Line Systemic Treatment?**

Sorafenib is the only approved systemic agent for the treatment of advanced HCC and there is a great unmet need for new, effective therapies for this condition. Although the clinical and molecular diversity of HCC poses a challenge for drug developers, several novel targets are undergoing evaluation, most notably hepatocyte growth factor receptor (MET).

Table 2 shows the recently published multicenter, double-blind, randomized, placebo-controlled phase III trials of potential second-line HCC treatments [28–30]. These trials evaluated two small molecules, brivanib and everolimus, and a monoclonal antibody, ramucirumab, and all failed to reach their endpoints. Interestingly, the REACH trial identified a pre-defined subpopulation, i.e., patients with high baseline alpha-fetoprotein values, who benefited from treatment with ramucirumab [31].

However, some important lessons were learned from these trials, and our understanding of liver cancer is evolving. Until recently, it was not clear how long patients well enough

<table>
<thead>
<tr>
<th>Table 1. Definition of TACE failure/refractoriness (LCSGJ)</th>
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<tbody>
<tr>
<td><strong>1. Intrahepatic lesion</strong></td>
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<tr>
<td>I. Two or more consecutive ineffective responses within the treated tumors (viable lesion &gt;50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery. The ineffective responses are determined by response evaluation CT/MRI images taken 1–3 months following adequately performed selective TACE.</td>
</tr>
<tr>
<td>II. Two or more consecutive progressions in the liver (tumor numbers even increase compared to the tumor numbers before the previous TACE procedure) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery. The progressions are detected on response evaluation CT/MRI images taken 1–3 months following adequately performed selective TACE.</td>
</tr>
<tr>
<td><strong>2. Tumor marker</strong></td>
</tr>
<tr>
<td><em>Continuous elevation of tumor markers</em> right after TACE even though transient minor reduction is observed.*</td>
</tr>
<tr>
<td><strong>3. Appearance of vascular invasion</strong></td>
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<tr>
<td><strong>4. Appearance of extrahepatic spread</strong></td>
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</table>
to participate in subsequent clinical trials survived after progression on sorafenib, making it difficult to interpret single-arm phase II trials. Now, it has been shown that, compared with patients ineligible for second-line trials, potentially eligible patients have a longer OS (median: 7.8–8.6 months), and this sets a new potential benchmark for assessing single-arm phase II studies [32]. Moreover, the high failure rate of HCC phase III trials results from the peculiar characteristics of this disease, such as the high rate of toxicity related to the underlying liver dysfunction, the challenges of discerning signals of efficacy from nonrandomized phase II data (because of uninformative surrogate endpoints and prognostic heterogeneity within clinical and biologic subsets), the imbalances in disease (liver-only versus metastatic spread), and patient characteristics (Child–Pugh class, cause of cirrhosis, ethnicity).

Taking a step back to early-phase trials, the development of the oral MET-inhibitor tivantinib may be taken as an informative example. First, two phase Ib studies in HCC [33, 34] and then a randomized placebo-controlled phase II study with extensive biomarker analysis were conducted [35, 36]. This phase II study defined MET expression as a prognostic factor for second-line treatment. The study reached its primary endpoint of time-to-progression in the overall population and reached the predefined secondary efficacy endpoints in MET-high patients, showing that high MET-expression identifies a group of patients who benefit most. This strategy for patient selection is being applied in the ongoing METIV-HCC phase III trial [37].

Metabolomics as single agent did not fare any better. In a randomized phase III study of ADI-PEG 20 arginine deaminase versus placebo, there was no difference in survival in between the two arms [38]. Future ADI-PEG 20 therapies will be based on combinatorial studies that would help enhance the activity of the drug.

Despite the discouraging outcomes of most recent studies, the latest have shown a more promising outcome. In a phase III trial, patients with advanced HCC who progressed on sorafenib were randomized to regorafenib, a similar mutli-tyrosine kinase versus placebo. The study showed an improvement in survival to 10.6 months versus 7.9 in favor of regorafenib. Further dissection of this positive outcome may be required considering the rather unrestricted short use of prior sorafenib, the requirement of prior sorafenib tolerance, and the randomization up to 10 weeks after sorafenib failure which all may suggest a selection bias for the population [39].

In conclusion, to develop an effective second-line systemic treatment for advanced HCC, we need to better understand the clinical and biologic factors that affect prognosis and response so as to facilitate stratification and biomarker enrichment strategies. Additionally, we need to change our approach to the development of systemic therapies. In fact, we can no longer proceed with phase III trials of experimental drugs unless they show statistically significantly advantages in randomized phase II trials or clinically meaningful benefits in Table 2. Second-line phase III trials in advanced HCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Principle target of experimental drug</th>
<th>No. of patients</th>
<th>Median OS</th>
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<tbody>
<tr>
<td>Brivanib versus placebo</td>
<td>VEGFR, FGFR</td>
<td>395</td>
<td>9.4 versus 8.2 months</td>
</tr>
<tr>
<td>(BRISK-PS)[28]</td>
<td></td>
<td></td>
<td>HR 0.89 (0.69–1.15), p=0.33</td>
</tr>
<tr>
<td>Everolimus versus placebo</td>
<td>mTOR</td>
<td>546</td>
<td>7.6 versus 7.3 months</td>
</tr>
<tr>
<td>(EVOLVE-1)[29]</td>
<td></td>
<td></td>
<td>HR 1.05 (0.86–1.27), p=0.68</td>
</tr>
<tr>
<td>Ramucirumab versus placebo</td>
<td>VEGFR2</td>
<td>565</td>
<td>9.2 versus 7.6 months</td>
</tr>
<tr>
<td>(REACH)[30]</td>
<td></td>
<td></td>
<td>HR 0.87 (0.72–1.05), p=0.14</td>
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VEGFR=vascular endothelial growth factor receptor; FGFR=fibroblast growth factor receptor; HR=hazard ratio; mTOR=mechanistic target of rapamycin.
nonrandomized phase II studies with an adequate number of homogeneous patients. Furthermore, the collection of biologic samples should become part of routine clinical practice to help identify and validate prognostic and predictive biomarkers (e.g., MET).

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