Regorafenib as Second-Line Systemic Therapy May Change the Treatment Strategy and Management Paradigm for Hepatocellular Carcinoma

Introduction

At the European Society of Medical Oncology World Congress of Gastrointestinal Cancer held in Barcelona, Spain, on 30th June 2016, positive outcomes were reported by the Study of Regorafenib after Sorafenib in Patients with Hepatocellular Carcinoma (RESORCE) trial, which investigated the efficacy of regorafenib as second-line therapy after sorafenib failure [1]. In this clinical trial, the group who received regorafenib achieved a survival benefit of approximately 2.8 months compared to the placebo group. Overall survival (OS) was 10.6 months in the regorafenib arm compared with 7.8 months in the placebo arm, with a hazard ratio (HR) of 0.62 (95% confidence interval [CI]: 0.50–0.78; p<0.001). These are groundbreaking results.

The positive outcome achieved by this second-line systemic therapy is a major development, especially after the numerous reports of failures in clinical studies of first- and second-line systemic therapeutic agents (table 1). Regorafenib therapy is expected to significantly prolong life expectancy by approximately 2.8 months in patients with hepatocellular carcinoma (HCC) who develop progressive disease (PD) during sorafenib therapy. This development will certainly lead to drastic changes in the treatment strategy and management paradigm for HCC.

Design of the RESORCE Trial

The RESORCE trial enrolled 573 patients with advanced HCC corresponding to Barcelona Clinic Liver Cancer (BCLC) stage B or C who were unresponsive to sorafenib. The patients were divided into placebo and regorafenib arms at a 1:2 ratio for the daily administration of placebo and oral regorafenib (160 mg), respectively, for three weeks on and one week off...
(four weeks/cycle) (fig. 1). Geographic region, performance status on the Eastern Cooperative Oncology Group scale, α-fetoprotein level (≥400 or <400 ng/mL), macrovascular invasion, and extrahepatic disease were used as allocation factors. This study excluded patients who were intolerant of sorafenib and who discontinued the treatment because of side effects. It enrolled only those patients who discontinued sorafenib because of evidence of PD on imaging studies. In addition, patients were included only if they had received ≥400 mg sorafenib for at least 20 of 28 days immediately prior to radiologically detected PD. In other words, this trial was designed (1) to ensure regorafenib tolerance among patients, and to reduce the occurrence of the drug-specific skin symptoms because the compound is structurally similar to sorafenib [2,3] (fig. 2) and (2) to reduce the effect of post-trial treatment on OS in both the placebo and treatment arms by using a homogeneous group of patients who developed PD due to sorafenib failure.

In general, post-progression survival (PPS) is defined as the time interval between the diagnosis of PD after primary treatment and the patient’s death, and OS is the sum of PPS and progression-free survival (PFS). Therefore, even significant differences in PFS can be canceled out because PPS is prolonged. Indeed, OS showed a stronger correlation with PPS than with PFS in a clinical trial of sorafenib [4]. Because HCC responds extremely well to locoregional therapy, it is often used as post-trial treatment even in cases in which locoregional therapy is no longer applicable and molecular targeted agents are subsequently administered in accordance with the protocol, provided that the patient’s general condition is stable. This rarely happens with other types of cancer and is therefore essentially unique to HCC, owing to the availability of powerful locoregional therapies such as intra-arterial infusion chemotherapy [5–7], transcatheter arterial chemoembolization (TACE) [8, 9], and radiofrequency ablation [10–12]. These post-trial treatments are capable of canceling out any difference in the primary endpoint OS by prolonging PPS [13]. Indeed, previous clinical trials of second-line agents other than regorafenib have always included patients intolerant

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**Table 1.** Phase III Clinical Trials of Japanese Participation for HCC

| Target population | Design                  | Trial name  | Presentation | Publication |
|-------------------|-------------------------|-------------|--------------|-------------|
| Early Adjuvant    | 1. Peretinoin vs Placebo* | NIK-333     | ASCO 2010    | JG 2014     |
| (prevention of recurrence) | 2. Sorafenib vs Placebo* | STORM       | ASCO 2014    | Lancet-O 2015 |
|                   | 3. Peretinoin vs Placebo | NIK-333/K-333 | Ongoing      |             |
| Intermediate Improvement of TACE | 1. TACE ± Sorafenib* | Post-TACE   | ASCO-GI 2010 | EJC 2011    |
|                   | 2. TACE ± Brivanib*     | BRISK-TA    | ILCA 2013    | Hepatol 2014 |
|                   | 3. TACE ± Orantinib*    | ORIENTAL    | EASL 2015    |             |
| Advanced First line | 1. Sorafenib vs Sunitinib* | SUN1170     | ASCO 2011    | JCO 2013    |
|                   | 2. Sorafenib vs Brivanib* | BRISK-FL    | AASLD 2012   | JCO 2013    |
|                   | 3. Sorafenib vs Linifanib* | LiGHT      | ASCO-GI 2013 | JCO 2015    |
|                   | 4. Sorafenib ± HAIC*    | SILIUS      | EASL 2016    |             |
|                   | 5. Sorafenib vs Nivolumab | REFLECT    | Ongoing      |             |
|                   | 6. Sorafenib vs Nivolumab | CheckMate 459 | Ongoing      |             |
| Second line       | 1. Brivanib vs Placebo* | BRISK-PS    | EASL 2012    | JCO 2013    |
|                   | 2. Everolimus vs Placebo* | EVOLVE-1    | ASCO-GI 2014 | JAMA 2014   |
|                   | 3. Ramucirumab vs Placebo* | REACH      | ESMO 2014    | Lancet-O 2015 |
|                   | 4. S-1 vs Placebo*      | S-CUBE      | ASCO 2015    |             |
|                   | 5. Regorafenib vs Placebo# | RESORCE   | WCCG 2016    |             |
|                   | 6. Tivantinib vs Placebo | JET-HCC     | Ongoing      |             |
|                   | 7. Ramucirumab vs Placebo | REACH-2    | Ongoing      |             |
|                   | 8. Pembrolizumab vs Placebo | KEYNOTE-240 | Ongoing      |             |

*Randomized controlled trial (RCT) halted or negative results. #RCT positive result. HAIC=Hepatic arterial infusion chemotherapy.
to sorafenib, which may have increased the influence of post-trial treatment and thus contributed to their negative outcomes. Patients unresponsive to sorafenib are those who develop PD during sorafenib therapy and are likely to have relatively poor hepatic function and overall general condition. By contrast, patients intolerant to sorafenib are those who discontinue the treatment because of side effects; these patients are in relatively stable conditions because of negligible amounts of internalized sorafenib, and a lack of HCC progression. Because of their clinical stability, patients intolerant to sorafenib are inevitably treated by locoregional therapy or various other post-trial treatments, including the re-administration of sorafenib, regardless of whether they received an actual second-line agent or placebo during the trial. With this in mind, clinical trials of second-line agents should enroll only patients who are unresponsive to sorafenib [14]. The RESORCE trial was the first clinical study to reflect this point in the trial design (fig. 1). The benefit of excluding patients intolerant to sorafenib was demonstrated in the subanalysis of a previous phase II study of axitinib, which generated an excellent HR and a significant study outcome [15, 16].

The second noteworthy point in the design of the RESORCE trial is that the allocation factors of macrovascular invasion and extrahepatic disease were treated as independent stratification factors. In general, the designs of previous clinical trials of molecular targeted agents involved allocation factors specifying “vascular invasion and/or extrahepatic spread” or “neither.” However, because vascular invasion is an extremely poor prognostic factor for HCC, assigning vascular invasion to the same category as extrahepatic spread may have influenced the outcome of these clinical trials. For example, when the treatment group contains more patients with vascular invasion but the placebo group includes more patients with extrahepatic spread, such sampling bias will put the treatment group at a significant disadvantage. In fact,
such allocation imbalance apparently contributed to a negative outcome in a clinical trial of brivanib as second-line therapy [17] (table 2).

The design of the RESORCE trial is excellent because it reflects what was learned from the negative outcomes of past trials and the reasons for those outcomes.

Fig. 2. Chemical structure of Regorafenib is very similar to that of Sorafenib.

Fig. 3. Switching from repeated TACE to sorafenib may prolong the survival of patients with HCC at the point of TACE failure/refractoriness. Reproduced with permission from Kudo M, et al. [23]
Results of the RESORCE Trial

In the RESORCE trial of regorafenib, the primary endpoint OS in the treatment group was favorable, with a HR of 0.62 relative to the placebo group (95% CI: 0.50–0.78; p<0.001). Despite being a second-line agent, regorafenib extended the median OS to 10.6 months compared with 7.8 months in the placebo arm, which was a groundbreaking result (table 3). PFS was 3.1 months in the regorafenib arm and 1.5 months in the placebo arm, with a HR of 0.46 (95% CI: 0.37–0.56; p<0.001). In addition, compared with 1.5 months in the placebo arm, regorafenib extended time to progression (TTP) to 3.2 months, with a HR of 0.44 (95% CI: 0.36–0.55; p<0.001). Furthermore, the disease control rate (DCR) was 65.2% in the regorafenib arm and 36.1% in the placebo arm, with a significant intergroup difference. Similarly, the overall response rate (ORR) was 10.6% in the regorafenib arm and 4.1% in the placebo arm, with a significant intergroup difference (table 3).
Impact of These Positive Results on HCC Management

To date, numerous clinical trials of second-line agents have failed to produce a good outcome (table 1), which makes the positive outcome of the phase III trial of regorafenib even more important. In the past, treatment strategies were designed without scientific evidence after first-line therapy with sorafenib because of the lack of second-line therapies with proven survival benefits. However, from now on, the survival of patients with advanced HCC can be improved by transitioning to second-line therapy with regorafenib. This will require the correct administration of sorafenib and a longer treatment period. There is no doubt that regorafenib will improve the prognosis of patients with advanced HCC even after the development of PD due to sorafenib failure, provided that sorafenib is administered properly.

Furthermore, sequential therapy with sorafenib and regorafenib will require re-establishing the appropriate timing of sorafenib administration. This is because transitioning to second-line therapy while maintaining Child-Pugh Class A liver function can be difficult if patients are treated with sorafenib for the first time after the HCC has progressed to an advanced stage.

What happens when sorafenib is administered to patients with intermediate-stage HCC? Conventionally, TACE is first-line treatment for intermediate-stage HCC [18]. Superselective TACE is regarded as an effective treatment method that can produce survival benefits and favorable response without adversely affecting hepatic functional reserve. Regarding patients with large-sized HCC or multiple bilobar nodules, these lesions are treated with repeated TACE, which seldom produces good results, or may even adversely affect hepatic functional reserve. Therefore, it will be important in the future to determine the optimal time to switch to sorafenib-regorafenib sequential therapy in patients who are unresponsive to TACE [19].

Systemic Therapy at the Point of TACE Failure/Refractoriness

The definition of TACE failure/refractoriness by the Japan Society of Hepatology was validated previously [20]. Two studies compared the prognosis of patients who switched to sorafenib therapy after confirmation of TACE failure/refractoriness to that of patients who continued to undergo repeated TACE [21, 22]. These studies showed that survival benefits were better in patients who switched to sorafenib therapy at the time of TACE failure/refractoriness [23] (fig. 3). This suggests that prognosis will be improved by accurately defining the time point of TACE failure/refractoriness in accordance with this definition and switching to systemic therapy with effective chemotherapeutic agents, namely, sorafenib and regorafenib. The positive outcome of the RESORCE trial underscores the importance of protocolizing the treatment for HCC such that when there is TACE failure/refractoriness, that the switch to systemic therapy is performed in a timely manner.

Indication of Systemic Therapy in BCLC B Substages

As previously reported in many studies, patients with BCLC stage B HCC constitute an extremely heterogeneous group that includes a subgroup of patients who are unresponsive to TACE (fig. 4). The patients unresponsive to TACE benefit more in terms of survival if they start sorafenib therapy without undergoing TACE. This should be investigated in the future by conducting a randomized clinical trial of TACE and systemic therapy. Specifically, the Kinki criteria classify BCLC stage B HCC, which is intermediate-stage HCC, into substages B1, B2,
and B3 [24, 25] (table 4). Compared with substage B1 HCC, TACE is clearly not effective in substage B2 HCC, which in turn often reduces hepatic functional reserve. Therefore, patients with substage B2 HCC may easily develop TACE unresponsiveness (fig. 4). Further studies should be aimed at determining whether this group of patients will benefit in terms of survival if they undergo systemic therapy either with targeted therapy or immune checkpoint inhibitors (table 5) [26] from the outset without TACE (fig. 5).

**Fig. 4.** Heterogeneity and treatment strategy of intermediate-stage HCC. Substage B2 may be a candidate for clinical trials of TACE combination therapy with tyrosine kinase inhibitors or immunotherapy. Modified with permission from Kudo M, et al. [25]

**Conclusion**

The positive results of the RESORCE trial will have a huge impact on the management of HCC. In particular, to obtain survival benefits from systemic therapy, it is necessary to determine the onset of TACE unresponsiveness or to identify patients with a HCC substage that is predisposed to TACE unresponsiveness, and then to initiate systemic therapy in these patients as early as possible. These issues should be clarified in future clinical trials.
### Table 4. Subclassification of Intermediate-Stage HCC: Kinki Criteria

| BCLC Substage | B1 | B2 | B3 |
|---------------|----|----|----|
| Child-Pugh score | 5–7 | 5–7 | 8–9 |
| Beyond Milan and up-to-7 criteria | IN | OUT | ANY |
| Sub-substage | | | |
| Concept of treatment strategy | Curative intent | Non-curative | Palliative |
| Treatment option | Resection | DEB-TACE (>6 cm) | Transplantation |
| | Ablation | HAIC (>6 tumors) | Ablation |
| | Superselective cTACE | Sorafenib (CP-A) | Superselective cTACE |
| | | | |
| Alternative | DEB-TACE (large, CP-7) | cTACE | DEB-TACE |
| | B-TACE (fewer tumors) | | B-TACE, HAIC |
| | | | |

**cTACE**=conventional transarterial chemoembolization using lipiodol mixed with anticancer drugs; **DEB**=drug-eluting bead; **B-TACE**=balloon-occluded transarterial chemoembolization; **CP**=Child-Pugh; **BSC**=best supportive care. Reproduced with permission from Kudo M, et al. [25]

### Table 5. Objective Response by Nivolumab

| Uninfected: Sorafenib Naïve/Intolerant (n=54) | Uninfected: Sorafenib Progressors (n=58) | HCV (n=51) | HBV (n=51) | Total (n=214) |
|-----------------------------------------------|------------------------------------------|-------------|-------------|---------------|
| Objective response, n (%)                     |                                          |             |             |               |
| Partial response                              | 0                                        | 2 (3)       | 0           | 2 (1)         |
| Stable disease                                | 32 (59)                                  | 27 (47)     | 29 (57)     | 111 (52)      |
| Progressive disease                           | 11 (20)                                  | 18 (31)     | 12 (24)     | 63 (29)       |
| Not evaluable                                 | 0                                        | 2 (3)       | 3 (6)       | 5 (2)         |

**HCV**=hepatitis C virus; **HBV**=hepatitis B virus. Reproduced with permission from El-Khoueiry AB, et al. [26]
Fig. 5. Treatment strategy for sorafenib-regorafenib sequential therapy. Identification of the subgroup that easily develops TACE failure/refractoriness may be important. For that subgroup, systemic therapy may be a more adequate treatment strategy than TACE for improving patient survival/benefit.

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