Editorial

A STORM in a teacup?—the challenges of adjuvant therapy in hepatocellular carcinoma (HCC)

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Globally, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death, with rising worldwide incidence (1). Surveillance programs for early detection of HCC in high-risk populations and improvement of therapeutic modalities have increased the likelihood of potentially curative treatments. Hepatic resection (HR) and radiofrequency ablation (RFA) result in 5-year survival rates of 40–70%. However, high tumor recurrence rates of 50% at 3 years and 70% at 5 years lead to sub-optimal curative outcomes (2).

The prevention of recurrent HCC remains a significant challenge in this population and has led to interest in the development of adjuvant therapies. The oral multikinase inhibitor sorafenib is approved in patients with unresectable HCC based on two pivotal phase 3 randomized trials (3,4). Sorafenib acts on multiple targets such as VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, Raf, RET, and FLT-3 (5) and has the dual antitumor effect of antiproliferation and antiangiogenesis. Since tumor recurrence is often predicated on the presence of vascular micro-invasion and micrometastases, these antitumor mechanisms provide rationale for the use of sorafenib as an adjuvant therapy.

Bruix *et al*. recently reported on the results of the STORM study, which assesses the utility of sorafenib as an adjuvant therapy following HCC treatment (6). This multinational trial enrolled HCC patients who had undergone curative therapy with HR or RFA within 4 months and had no radiological evidence of residual tumor. Subjects were required to have baseline alpha-fetoprotein (AFP) level under 400 ng/mL, preserved performance status (Eastern Cooperative Oncology Group score of 0/hepatic synthetic function (Child Pugh score 5–7, Child-Pugh score 7 allowed only in the absence of ascites) and intermediate to high risk of recurrence [stratification based on pathological tumor characteristics (following HR) or imaging criteria (following RFA)]. The primary outcome measure was recurrence-free survival (RFS); secondary endpoints were time to recurrence and overall survival (OS). After a median follow up of 8.45 months (range, 2.9–29.8 months) there was no significant difference in RFS, time to recurrence or OS in the sorafenib treated group compared to placebo.

How can we best explain the lack of benefit seen with sorafenib adjuvant therapy in this study? One possible explanation is the unexpectedly high rate of treatment discontinuation, and consequently fewer recurrence events than expected. The number of subjects discontinuing sorafenib (50% at 1 year) was higher than noted in other studies and may represent a lower threshold of tolerance for a drug considered to be an adjunctive rather than primary form of therapy, although the reported grade 3 or 4 toxicities were not too different compared to the toxicities observed in other studies. The statistical analysis was adjusted to reflect the fewer recurrence events reported as a result of higher than expected treatment discontinuation by reducing the power from 90% to 80%. Additionally, sorafenib dose reduction was required in 79% of subjects resulting in a mean daily dose of sorafenib (578 mg) much lower than the intended 800 mg dose. This dose reduction is in contrast to the SHARP study in which 76% of subjects received more than 80% of the planned dose.

Interestingly, the median treatment duration in the sorafenib groups was shortest in the Americas. This is the region in which the majority of HCC was related

to hepatitis C virus (HCV). It has been recognized that HCV-related HCC has a better response to sorafenib; therefore decreased exposure to sorafenib may have disproportionately affected this group. The recurrence rates in this study were also lower than reported in the scientific literature, which may reflect the rigorous selection criteria required for entry into the study such as an AFP cut-off, which may have excluded patients with disease undetectable by imaging; and careful, protocol based imaging, that possibly excluded patients with undetected tumoral remains after treatment.

The risk stratification system utilized by the authors merits discussion. Criteria for the high risk group, including microvascular invasion, satellite tumors/multifocal disease, or poorly differentiated tumor grade have been recognized to increase the risk of cancer recurrence. However, criteria for the intermediate risk group defined as a single tumor of 2 cm or larger with well differentiated or moderately differentiated microscopic appearance, have not been validated as a strong predictor for cancer recurrence in other studies, especially within the first year following resection.

It is not therefore not clear that this risk stratification was able to accurately discern between differing risks of recurrence and it is possible that a fraction of the subjects were not intermediate/high risk as assumed by study design, but instead were at low risk of recurrence.

Most importantly, the signaling pathways involved in the mechanisms of HCC recurrence may be different from those involved in de novo carcinogenesis and have not been well-defined. While proliferation and angiogenesis, which are the pathways primarily affected by sorafenib, are important in HCC progression, their role in recurrence is less clear. Sorafenib is also recognized to influence the tumor microenvironment by its effect on hepatic stellate cells and Kuppfer cells. However, the composition of this microenvironment in recurrent disease is poorly described and may be less influenced by sorafenib.

Adjuvant therapy in HCC following curative treatment thus remains an unmet need. In much of the world, HCC is a consequence of viral hepatitis. New and highly effective therapies for hepatitis C will no doubt impact the future burden of this disease. In terms of hepatitis B, a recent meta-analysis of nucleotide therapy following curative therapies found that antiviral treatment significantly improved RFS and OS (7). There have been multiple approaches to adjunctive therapy such as the use of angiotensin receptor blockers (8) as well as standard chemotherapy. A recent randomized controlled trial has demonstrated that postoperative adjuvant chemotherapy with capecitabine reduced the risk of recurrence and tends to improve postoperative survival of HCC (9). This study is limited by its relatively small sample size.

A novel approach is the use of adjunctive immunotherapy, which has been explored in a recent study in HCC patients after microwave ablation (MWA) (10). Even though the rate of disease-free survival and OS within 16 months of MWA did not differ significantly between the two groups, the immune status and liver function of these patients did improve. An alternate immunologic approach involves the use of dendritic cell vaccines pulsed with various tumor antigens (11). This was recently studied in 12 patients following primary curative therapy: 9 of 12 showed no tumor recurrence. While these are promising early results, much work remains to be done to elucidate the mechanisms and efficacy of immunologic therapy in HCC.

In conclusion, the STORM study has further expanded our understanding of the challenges and opportunities inherent in the treatment of HCC in the adjuvant setting. While no definite benefit could be demonstrated by the use of sorafenib as adjuvant therapy, this large, well-conducted international trial provides us with a wealth of useful information about the differing manifestations of this heterogenous tumor and offers useful insights into the design of future adjuvant HCC studies. Most importantly, this study provides further validation that HCC is a complex oncologic entity requiring multidisciplinary approaches and multifaceted therapies, and is best managed in a collaborative manner involving several specialized services.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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