Second-line Therapies in Hepatocellular Carcinoma: Emergence of Resistance to Sorafenib

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Second-line therapies are needed for patients with advanced hepatocellular carcinoma who progress after sorafenib. Positive signals seen with brivanib in phase II studies, reported herein, have yet to be confirmed in phase III trials. Identification of the molecular mechanisms driving sorafenib resistance should guide drug development strategies in this setting. Clin Cancer Res; 18(7); 1824–6. ©2012 AACR.
studies to accurately capture signals of efficacy and provide reliable assumptions for trial design (7). Two phase III trials in the second-line setting are still ongoing, testing either everolimus (mTOR inhibitor) or ramucirumab (VEGFR2 monoclonal antibody); these trials will be informative. The negative result reported here adds to the recent failure of sunitinib as a first-line treatment (6) and further highlights the complexity of advancing the field of systemic treatment for patients with advanced HCC.

In 2003, the U.S. Food and Drug Administration approved the first molecular-targeted agent for a solid tumor (the EGFR inhibitor gefitinib in lung cancer). The development of this new family of drugs has dominated translational research in oncology during the past decade. Previous results of imatinib in chronic myeloid leukemia set high expectations for targeted therapies for solid tumors (8). Imatinib was able to induce remarkable clinical remissions by blocking the activity of the BCR–ABL fusion protein, the known molecular substrate of the disease. As a conceptual consequence, the rationale behind molecular therapies was not to target the molecular aberrations present in tumors, but to preferentially antagonize alterations implicated in tumor progression (“oncogene addiction”). Some recent successes using this approach include vemurafenib in BRAF-mutated melanomas (9) or crizotinib in lung tumors with ALK rearrangements (10). Unfortunately, the distinction between driver and passenger events in solid tumors is only beginning to be translated into clinical medicine. To date, potential drivers of oncogenic addiction have not been explored in the HCC clinical setting by trial enrichment, either because of a lack of reliable biomarkers or because of a marginal interest in expensive explorations of small niches of patients with good responses.

The high molecular heterogeneity in HCC favors deregulation of multiple drivers, increasing the odds that a drug with a wider kinase blockade spectrum may be effective; such is the case of sorafenib. Our limited understanding of the mechanism of action of sorafenib in advanced HCC, however, makes it even more difficult to determine the possible resistance mechanisms. Preclinical models suggested that phenotypic resistance to VEGFR inhibition could induce activation of VEGF-independent angiogenic signals, by members of the FGF family (11). In addition, genomic and functional studies indicated that FGF19 could act as an oncogenic driver in HCC (12, 13). Together, these data provided sufficient rationale to test FGFR inhibition in patients with sorafenib-resistant HCC. Increased understanding of the final results of the phase III trial will determine the role of brivanib as second-line therapy. However, it seems clear that mechanisms of resistance to...
sorafenib include both FGFR-dependent and -independent pathways.

In the past 2 years, 2 studies testing molecular therapies did not reach the primary endpoint in first- and second-line settings for HCC. Several drugs with new targets are under evaluation in phase II and III trials (3). All of these agents need to balance efficacy with the true bottleneck of trial success in cirrhotic patients, which is toxicity. In fact, safety profiles were among the main issues jeopardizing trial success in 1 of the 2 cases in which results did not meet the primary endpoint (i.e., sunitinib). This finding suggests that the management and trial design of HCC may be unique in oncology. Alternatively, other backup strategies in drug development have to be taken into account; this requires a better understanding of the molecular pathogenesis of disease progression and resistance to sorafenib (Fig. 1). The development of targets based on their ability to behave as oncogenic addiction loops and the implementation of clinical trials designed to enrich populations, based on molecular biomarkers of these events, should move the field forward. The success of trial enrichment based on molecular biomarkers in other solid tumors encourages these types of approaches (12, 13).

Disclosure of Potential Conflicts of Interest

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