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LETTERS TO THE EDITOR

Tumor biopsy and patient enrollment in clinical trials for advanced hepatocellular carcinoma

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Abstract

Tumor biopsies may help to reliably distinguish hepatocellular carcinoma (HCC) from other tumors, mostly cholangiocarcinoma as well as to identify the patient populations who most benefit from target-driven HCC treatments, in order to improve the success rate of experimental therapies. Clarifying tumor biology may also lead to identify biomarkers with prognostic role and/or enabling to predict response or resistance to therapies. Recently, clinical trials have more efficiently included biomarker endpoints and increasingly collected tumor tissue from enrolled patients. Due to their frail status and sometimes fast-progressing disease, the performance status of patients with HCC progressing on first-line therapy can deteriorate quickly, preventing their enrollment in clinical trials. However, the challenge of identifying the proper patient at the proper time can be overcome by periodic inter-department meetings involving the key specialists taking care of HCC patients, and solid networks between research centers and referring institutions. An early planned biopsy would also facilitate timely inclusion of patients in biology-driven clinical trials. Ultimately, institution of multidisciplinary teams can optimize treatment choice, biopsy timing, and quick enrollment of patients in clinical trials, before their performance status deteriorates.

Key words: Liver neoplasms; Biopsy; Biomarkers; Clinical trial; Tumor

Core tip: Despite the extensive research conducted in the last two decades, still only two agents have shown positive results in phase III clinical trials for advanced hepatocellular carcinoma, and clinicians have no way to predict which patient population will benefit more. Biomarker research and well-run clinical trials require biopsies and a multidisciplinary approach to manage patients with hepatocellular carcinoma.

Rimassa L, Reig M, Abbadessa G, Peck-Radosavljevic M, Harris W, Zagonel V, Pastorelli D, Rota Caremoli E, Porta C, Damjanov N, Patel H, Daniele B, Lamar M, Schwartz B, Goldberg T, Santoro A, Bruix J. Tumor biopsy and patient enrollment in clinical trials for advanced hepatocellular carcinoma. *World J Gastroenterol* 2017; 23(13): 2448-2452 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i13/2448.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i13.2448

TO THE EDITOR

Liver cancer was estimated to be responsible for almost 746000 deaths worldwide in 2012 (WHO), with hepatocellular carcinoma (HCC) being the most common type[1]. Sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), is the only approved first-line systemic therapy for HCC[2,3]. Recently regorafenib, a similar multi-targeted TKI, was shown to benefit HCC patients who tolerated and progressed on sorafenib[4]. It is still unclear which patient sub-populations may benefit more from these drugs although interestingly, development of dermatological adverse events and AFP decrease during treatment may be associated with improved outcomes on sorafenib[5,6].

Many efforts to develop new therapies for unselected HCC populations have failed: in first-line, sunitinib[7], brivanib[8], linifanib[9] when compared to sorafenib; and erlotinib[10] and doxorubicin[11] in combination with sorafenib; in second-line, brivanib[12], everolimus[13], ramucirumab[14], and ADI-PEG 20[15]. Studies looking for alternative approaches for HCC, such as immunotherapy, are ongoing[16,17].

While for other solid tumors prognostic and predictive molecular biomarkers are already used in clinical practice, for HCC biomarker research has not produced conclusive results[18-20]. The many disappointing clinical trial failures due to excessive toxicity, lack of efficacy, study design problems, or lack of biological population enrichment, emphasize the need to identify predictive molecular biomarkers for selection of treatment in patients with HCC.

Circulating biomarker analyses from the sorafenib approval study suggested that the angiogenesis biomarkers angiopoietin-2 (Ang2) and vascular endothelial growth factor (VEGF) were independent prognostic factors, while none of the tested biomarkers were predictive of sorafenib efficacy[21]. On the contrary, on the basis of positive efficacy and biomarker results in tumor MMNG HOS transforming gene (MET)-High patients in a randomized phase II study[22,23], tivantinib has been tested in two phase III studies selecting only MET-High patients, one in western countries and the other in Japan (NCT01755767, NCT02029157); while the study in the western world has recently been announced to be negative[24], results are still awaited for the Japanese study. Recently, second-line ramucirumab was shown to offer a significant survival benefit in a pre-specified subgroup of patients with elevated alpha-fetoprotein (AFP)[14] and a confirmatory phase III clinical trial is ongoing in this sub-population (NCT02435433).

Challenges of enrolling patients into clinical trials for second-line HCC

Most patients with advanced, unresectable HCC who are eligible for clinical trials with systemic therapies have a

relatively short life expectancy, with rapid progression of disease, especially if they have progressed on sorafenib and have distant metastases[25,26]. To optimize timely and proper recommendations for the care of these patients, their cases should be discussed periodically by multidisciplinary teams including medical oncologists, gastroenterologists/hepatologists, surgeons, interventional radiologists, radiation oncologists, and pathologists. Such meetings would ideally take place weekly, or every two weeks: a longer delay of the proper therapeutic decision may undermine the possibilities of trial enrolment for patients.

Patients who are not followed in research centers may find it challenging to seek further treatment options, other than best supportive care, after failing standard treatments. On the other hand, many physicians have difficulties in identifying proper patients for second line clinical trials. Set up of webpages listing available clinical trials, and of inter-hospital networks to prime referrals for research studies can provide a key support to reduce the gap time for the comprehensive evaluation of these patients and speed up recruitment. Considering all this, with due exceptions, the best hospitals to involve in clinical trials for second-line HCC and to refer these patients to seem to be the larger academic centers, where HCC care is jointly pursued by at least oncologists and hepatologists.

Finally, study characteristics can make a difference in enabling trial enrolment, and involvement of active investigators from multiple relevant disciplines in the early phases of the protocol design can be beneficial to the scope.

Importance of analyzing tumor biomarkers to guide development of novel therapies

Analyzing HCC tumor specimens is essential to improve the knowledge about development, biology underpinning progression and treatment of HCC. Particularly, clarifying the tumor biology may lead to identifying biomarkers that would predict response or resistance to therapies.

Hepatology guidelines recommend that the diagnosis of HCC may be established *via* radiographic studies in the appropriate patient population[27], therefore not all patients with hepatic tumors have available biopsy material allowing for molecular profiling of their disease, at diagnosis. Furthermore, as tumors progress, they accumulate genetic alterations developing heterogeneity and drug resistance[28]. Studies suggest that VEGF pathway inhibition, as with sorafenib, produces a hypoxic microenvironment with oxidative stress that selects for highly aggressive, invasive tumor cells driving overexpression of proliferation factors, HCC progression, and induction of an immunosuppressive microenvironment[29,30]. Therefore, if in the future any molecular classifiers have an impact in clinical decision making, routine biopsy will become part of the standard of care. Considering the current treatment landscape, it seems rationale to biopsy patients with the purpose of including them in research studies. In the advanced disease setting, the risks associated with biopsy are minimal: seeding is rare and its consequences are irrelevant given the dismal prognosis of these patients, while bleeding is extremely rare especially if biopsy is conducted at an expert center with appropriate precautions particularly for superficial lesions. Considering the above and the general worsening of condition for many patients failing sorafenib, biopsies need to be planned ahead of time and be performed right at progression on sorafenib in order to be useful for trial enrolment.

Adequacy of tumor samples is a practical problem for clinical trials: shipment of not enough slides, or slides not containing enough tumor, causes unnecessary and significant delays to patient enrolment, particularly for patients from referring centers.

A core needle biopsy may be preferred to fine needle aspirates to provide quantitatively and qualitatively adequate material for running biological analyses on the sample. The procedure needs to take enough tumor material for at least 7-10 slides, the minimum generally needed for patient evaluation in clinical trial protocols. Slides from paraffin-embedded samples need to be unstained to allow immunohistochemistry testing. The operator performing the biopsy needs to be informed that the sample is being taken not only for diagnostic but also for biological assessments, and the pathologist needs to verify that all provided slides include sufficient tumor quantities.

A number of targeted agents are being tested in phase Ⅲ clinical trials in first- or second-line HCC: nivolumab [first line, anti-programmed cell-death protein 1 (PD1) antibody], tivantinib (second line, MET inhibitor), cabozantinib (second line, VEGF-MET inhibitor), ramucirumab (second line, anti-VEGF antibody), and pembrolizumab (second line, anti-PD1 antibody). While only tivantinib (in tumor MET-High patients) and ramucirumab (in circulating AFP-High patients) are being tested in biomarker-selected patient populations, other trials are collecting tumor tissue for biomarker analyses as secondary study endpoint, emphasizing the importance of tumor tissue biopsies for patients to be enrolled in clinical trials.

In conclusion, since the approval of sorafenib in first-line, while recent data demonstrated benefit of lenvatinib (VEGFR inhibitor) in first-line[31] and regorafenib in second-line setting, ten phase III studies in HCC were negative including sunitinib, linifanib, brivanib (first and second line), ramucirumab, everolimus, ADI-PEG 20, erlotinib (in combination with sorafenib), doxorubicin (in combination with sorafenib), and tivantinib (in western patients). All these studies were conducted in unselected patient populations, except the tivantinib one.

If the research community was able to bring targeted therapies to late stage development with solid preclinical

and clinical rationale to select patient populations based on the drug target, success rate might increase and adverse events would be avoided to patient populations estimated not to benefit from the experimental drug. Biological understanding of the treated population can be relevant even in trials where the target expression is not used as an entry criterion, providing key information to design subsequent target-selected studies. The historically low rates of biopsy confirmation of patients with HCC has presented a barrier to development of experimental therapeutics in this disease. With such frail patient population, multidisciplinary case discussions and inter-hospital networks can enable a seamless transition from standard care to tumor biology analysis for a clinical trial. Hopefully, as more targeted therapies are developed, the biological characteristics of tumors, including histology and more specific molecular markers, will be evaluated in the therapeutic decision process for HCC patients as currently occurs for other tumor types.

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