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World Journal of Gastroenterology (WJG) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Science Citation Index Expanded (also known as SciSearch®)

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All instructions are available online at http://www.wjgnet.com/bpg/guidelinets/204

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

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Author contributions: Rimassa L, Reig M, Abbadesa G, Santoro A and Bruix J wrote the manuscript; Peck-Radosavljevic M, Harris W, Zagonel V, Pastorelli D, Rota Caremoli E, Porta C, Damjanov N, Patel H, Daniele B, Lamar M, Schwartz B and Goldberg T contributed to the preparation, editing, and final approval of the manuscript.

Conflict-of-interest statement: Authors report no conflict of interest with the subject discussed in this article.

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Manuscript source: Unsolicited manuscript

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Received: January 20, 2017
Peer-review started: January 22, 2017
First decision: February 10, 2017
Revised: February 24, 2017
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

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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.
relatively short life expectancy, with rapid progression of
disease, especially if they have progressed on sorafenib
and have distant metastases\textsuperscript{[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, inter-
ventional 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 under-
pinning 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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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 appro-
priate 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
element, 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
tefaroferitinib (VEGFR inhibitor) in first-line\textsuperscript{[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),
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.

ACKNOWLEDGMENTS

We thank Hazem Hallak (CHEMC Global llc, Philadelphia, PA, United States) for his medical editorial assistance, and Kathleen Farren (ArQuel) for her editorial assistance.

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P- Reviewer: Gkretsi V, Varona MA S- Editor: Qi Y L- Editor: A E- Editor: Zhang FF