Editorial

Hot topics in hepatocellular carcinoma

Luca Ielasi, Elisabetta Goio, Francesco Tovoli

Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Correspondence to: Luca Ielasi. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. Email: luca.ielasi.kr@gmail.com.

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Hepatocellular carcinoma (HCC) is currently the second cause of cancer-related death worldwide and its incidence has been estimated to increase of about 20% by 2020 (1).

These dramatic epidemiology features are responsible for the increasing interest in finding effective preventive and therapeutic strategies. In the last years many efforts have been put in the primary prevention of HCC and in the improvement of therapeutic options. It is therefore unsurprising that many hot topics have risen and are currently at the centre of an intense debate.

When it comes to the primary prevention of HCC, interventions toward the most prevalent risk factors have to be considered. The development and the subsequent widespread availability of effective anti-hepatitis B virus (HBV) drugs and vaccination left hepatitis C virus (HCV) infection and non-alcoholic fatty liver disease (NAFLD) as the main causes of HCC with unmet needs. Until now, HCV infection has been the leading cause of liver cirrhosis and HCC in Western population (1). The advent of direct antiviral agents (DAAs) with high efficacy in achieving sustained virological response (SVR) is now expected to reduce the incidence of *de novo* HCC in patients with eradicated HCV infection. Unfortunately, after post-marketing surveillance, an SVR following DAAs seemed to be associated with a higher occurrence of *de novo* HCC and recurrence after HCC treated with curative therapies (2,3). Also, post-DAAs HCC seemed to show aggressive features with limited possibilities of receiving curative treatments (2). So far, two large prospective studies have been performed to verify these concerning reports (4,5). The results of these studies do not confirm the initial reports, observing a not increased risk of HCC in patients who underwent curative treatments, including liver transplantation. Moreover, SVR, obtained either with DAAs or interferon, was the pivotal factor in reducing cancer risk (4). Other recent studies suggested that DAAs do not impact on tumor aggressiveness (instead improving the early post-operative outcome) (6) and that biannual ultrasonography screening for HCC is highly expensive and little effective in non-cirrhotic patients receiving DAAs (7). So, which results should we trust about DAAs and risk of HCC? Serio *et al.* provide an extensive review of the current literature in this Special Issue to update the readers of *Translational Cancer Research*. In any case, prospective studies with a long-term follow up will be pivotal in settling the existing doubts (8).

Associated with the obesity and diabetes epidemics, NAFLD is becoming the leading cause of chronic liver disease in Western countries. NAFLD is an attributable cause of HCC, even before the development of cirrhosis (9). Effective strategies for identification of high-risk patients are urgently needed and represent a second hot topic in HCC. In the absence of strong and established evidences, most international guidelines do not support a widespread screening in these patients (10). Innovative biomarkers could help both in understanding the elusive pathogenesis of NAFLD-related HCC and in selecting particularly high-risk patients.

Therapeutic options are another debated topic in HCC. The existence of multiple international guidelines reflects different proposed strategies, even if actual discordances are limited (11). Medical community has always strived for better defining the indications for surgical and loco-regional approaches, but one of the hardest challenges of the last decade involved the complex field of advanced HCC. After the approval of sorafenib, a series of trials of systemic treatments failed. In the last two years, four new molecules have shown efficacy. Regorafenib (12), cabozantinib (13), and ramucirumab (14) were superior to placebo in patients failing sorafenib (with regorafenib tested only in patients who withdrawn sorafenib for progressive

disease, and ramucirumab effective only in patient with alfa-fetoprotein >400 ng/mL). Also, lenvatinib was found to be non-inferior to sorafenib as first line therapy (15). Immunotherapy trials are showing promising results as well (16), leading to an early registration of nivolumab by the US Food & Drug Administration. The updated scenario of post-sorafenib treatments has been thoroughly reviewed by Nenu *et al.* for the readers of this special issue (17). The hottest topic in this field regards the search for biomarkers. Further knowledge is in fact needed to clarify which patients will possibly benefit from the agents of different classes (tyrosine kinase inhibitors and immune checkpoint inhibitors), helping both in the daily clinical practice and in the design of the trials (18). New locoregional techniques for the control of locally advanced HCC have been also studied in the latest years. Selective internal radiation therapy, also called transarterial radioembolisation (TARE), is based on the use of microspheres containing radioactive substances, first of all yttrium-90 (19). Preliminary experience in patients with neoplastic portal vein invasion led to the creation of a number of clinical trials about TARE. Expectations were frustrated by the failed SARAH (20) and SIRVENIB (21) trials, which did not find a benefit of TARE compared to sorafenib both in per-protocol and intention-to-treat analyses. Even more hope was placed in the SORAMIC trial, which investigated whether the combination of TARE + sorafenib was superior to sorafenib alone. Unfortunately, the results of this trial have been presented at an international liver congress and were equally disappointing (22). The next years will be crucial to understand if highly debated elements in the design of the SARAH and SIRENIB trials may have influenced the outcome. These factors include the relatively low experience in the use of TARE of some recruiting centers or the possibility to include also patients with high burden of disease (for instance neoplastic invasion of the main portal trunk) which were less likely to receive an adequate and nontoxic radiation dose).

In conclusion, last years have been characterized by an exponential increase in knowledge concerning the optimal clinical approach of patients at risk of or affected by HCC, but this liver tumor is still a serious global public health problem. Research in this area is far from being over.

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