Hepatocellular carcinoma: the way done and what remains to be done

Hepatocellular carcinoma (HCC) is today one of the most common cancers in the world. There is solid evidence that chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse, workplace or environmental exposure to toxic substances, obesity, liver steatosis, non-alcoholic steatohepatitis (NASH) and liver cirrhosis are risk factors for the development of HCC. In particular, the liver cirrhosis represents an independent risk factor for HCC whatever the cause it has been determined (1-6).

Today a lot of knowledge has been acquired on epidemiology, on etiological factors and molecular mechanisms that contribute to the development of HCC, but it will be required that the research community has more ambitious targets in terms of prevention, early diagnosis, molecular typing of various types of HCC. In fact, today it is unthinkable to consider the HCC as one entity; often in a patient with multifocal HCC, single nodule phenotypic features differ from those of the other nodules and it is also possible that the single nodule has some cell groups with cancerous features different from one to another. All this shows that all HCC are not equal and also in the same subject HCC may present different characteristics. Phenotypic diversity is probably a different flaw or molecular aberration that affects its speed of growth, invasiveness and probably response to therapy (7).

Some HCC staging systems have been validated such as the Barcelona Clinic Liver Cancer (BCLC) staging system which predict patient survival and/or define her prognosis and also it helps to identify the best treatment strategy for each patient; and the Milan criteria that select patients with HCC who may undergo a liver transplant. Perfectible in light of new knowledge, such systems have represented a real chance to define as correctly as possible the stage of the tumor disease, and they have permitted the best treatment approach for the patient (8,9).

The study of molecular alterations in HCC has made possible to identify many signaling pathways, but the failure of many molecular therapies in phase II and III of clinical studies shows that many others will have to discover to get the most effective alternative therapist targets and systemic treatment of advanced HCC (C) according to BCLC staging system, probably these treatments will cover the combined use of different drugs target (targeted therapy) (7,8).

The relationship between the immune system and the development of HCC have been recently highlighted and it seems to get more and more important the role of the microenvironment as a factor that encourages tumor growth and its lack of recognition by the immune system (10,11).

It was found that some cancer biomarkers used in the diagnosis of HCC, such as des-gamma carboxy protrombina (DPC), the glypican-3 (GPC3) play an important role in the growth and invasion ability of HCC, playing the role of growth factors with apocrine and eccrine and capacity factors that promote tumor angiogenesis. In fact, the GPC3 is able to amplify the Wnt/Yap signaling and the DPC to activate the kinase insert domain receptor-DCP-phospholipaseC-γ-MAPK pathway, and the Ras/Raf/MEK/ERK signaling and Ras/PI3K/Akt/mTOR pathway cascades (12-19). Furthermore, recent researches indicate that DCP antagonizes the inhibitory effects of Sorafenib on HCC by the activation of the Ras/Raf/MEK/ERK and PI3K/Akt/mTOR/Ras signaling pathways (20).

Today these findings allow to classify the tumor based on the biomarker that it produces, and hopefully in the very next future, the antibodies and drugs can be synthesized to block the effects that biomarkers have on growth and on tumor invasion ability and resistance to therapy.

Recently the article of Reig M. and coauthors in Journal of Hepatolology 2016 October (21) has generated some worries in the scientific community. The authors show an “unexpected” rate in early recurrence of HCC in subject with HCV infections with HCC history treated with complete respond and absence of HCC nodules from the beginning of anti-HCV treatment with Direct-Acting Antiviral Agents (DAAS). Reig et al. report an HCC recurrence rate of 27.6% after a median follow up of 5.7 months (range 0.4 -14.6) from the beginning of treatment with DAAs and conclude by stating that cancer recurrence coincides with the clearance of HCV.

The conclusions by Reig M. and coauthors (21) have been evaluated and commented by Cammà C. et al. (22). They
Indicate some problems that we share: the small sample size studied, the wide confidence interval (CI) of 95% which is obviously expected due to the small sample size of the study, having reported the crude rate rather than the entire Kaplan-Meier Curve (K-M), the different clinical features of patients (HCC single vs. multinodular), the different treatments of HCC (resection, ablation and TACE), the wide interval of time between the treatment of HCC and the initiation of therapy with DAAs (median 11.2 months; range 1.2-87.7 months). Cammà C. et al. (22) correctly consider the start of K-M curve the moment of HCC treatment not the beginning of the therapy, it determines from 6 to 12 months of recurrence rate respectively from 7% and 13% not taking into consideration the crude data of 27.6%.

Moreover, other considerations have been moved by Torres HA et al. (23) and especially the fact that some patients have had a HCC recurrence 2 weeks after the start of a therapy with DAAs; it is an inexplicable case with the possible effect that DAAs would have had on the host immune respond, as supposed by Reig M and coauthors.

It is possible, however, that the HCC was already present and not still diagnosable at the beginning of therapy and its development was reasonably foreseeable in subjects already treated for HCC and where HCC little eradication could affect cancer recurrence.

Future studies on large series will give a definitive answer about the effect that the DAAs have on the development of HCC and definitely a real prevention of HCC can be achieved from advocated use of DAAs in mild liver disease patients without cirrhosis (24).

In conclusion, with the evidence we have, we may say that the defeat of HCC consists in the elimination of risk factors, early diagnosis and the inevitable necessity of classification of HCC based on molecular alterations; and therefore, in the near future the possibility of using target drugs for different types of HCC which are probably linked each other. Modulate the immune system and intervene on the microenvironment is the next challenge and it will move probably towards a multidisciplinary approach to the treatment of HCC which will consider surgical treatments of lesions, and in selected cases, liver transplants (25).

Acknowledgements
None.

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

References

Gaetano Bertino
Hepatology Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy.
(Email: gaetanobertinounic@gmail.com)

Michele Malaguarnera
Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy.

Giulia Malaguarnera
Research Center “The Great Senescence”, University of Catania, Catania, Italy.
(Email: giulia.malaguarnera@live.it)