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EDITORIAL

Hepatocellular Carcinoma: Portuguese Data in Chronic Hepatitis B Patients on Antiviral Therapy and Treatment Results With Sorafenib

Carcinoma Hepatocelular: Dados Portugueses de Doentes com Hepatite B Crónica sob Terapêutica Antiviral e do Tratamento com Sorafenib

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Liver cancer is the fifth most common malignant tumor in men and the ninth in women. An estimated 782,500 new cases occurred in the world during 2012.[1] Most primary liver cancers worldwide are hepatocellular carcinoma (HCC), which likely accounts for 70–90% of cases. Globally it is the second leading cause of cancer death in men and the sixth among women, with about 745,500 deaths in 2012.[1] It is one of the most fatal cancers, with five-year survival rates less than 20% even in developed countries.

HCC incidence is increasing in areas with historically low rates, including parts of Oceania, Western Europe, and Northern America. In the United States, age-adjusted incidence rates of liver cancer more than tripled between 1975 and 2011.[2]

This increase is thought to be attributable to chronic hepatitis C virus (HCV) infection, mainly due to injection drug abuse, which was common in the 1960s and 1970s, and also to increases in the prevalence of obesity and diabetes mellitus.[3,4] In Portugal, Marinho et al. revealed a 2.9-fold increase in hospital admissions for HCC in the twelve years studied (1993–2005), reaching 834 hospital admissions in 2005 (8.6/105).[5]

HCC is strongly associated with chronic hepatitis B virus (HBV) or HCV infections. Other risk factors include alcoholic cirrhosis (very important in our country), smoking, type 2 diabetes, and/or non-alcoholic fatty liver disease (associated with obesity).

The primary causes of HCC can be prevented through public health measures, which include avoiding smoking and limiting alcohol consumption, HBV vaccination, sanitary medical practices, healthy lifestyle choices, and environmental management strategies. A vaccine that protects against HBV has been available since 1982, and proved to be also an anti-tumoral vaccine. While there is no vaccine available to protect against HCV, new antiviral therapies may prevent chronic infection among those with acute (new) infection. The United States Center for Disease Control and Prevention recommends a one-time test for HCV infection for all adults born between 1945 and 1965, since people in this birth cohort account for three quarters of both HCV-infected individuals and HCV-related deaths in the United States.[6]

Among individuals with chronic viral hepatitis, a reduction in the progression of liver fibrosis, or even its regression, and also a reduction in the risk of liver cancer, has been shown with the use of antiviral treatments, mainly in HCV, but probably also in HBV infection.[4,7] Nevertheless, maintained surveillance of HCC occurrence is recommended in appropriate patients by the international guidelines.

Magalhães-Costa et al. publish in this issue of GE a paper which investigates HCC incidence, risk factors and

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the performance of baseline Risk estimation for hepatocellular carcinoma (REACH-B) score in a Portuguese population with chronic hepatits B on antiviral therapy. They retrospectively studied one hundred and twenty patients treated with tenofovir or entecavir for at least 12 months. The calculated cumulative incidence rates of HCC at 1, 3 and 5 years on therapy were 5.1%, 7.3% and 8.8%, respectively. Old age, excessive alcohol intake and cirrhosis were the most important risk factors associated with HCC onset. The discriminatory performance of baseline REACH-B score in those Portuguese patients was limited. The authors concluded that continued surveillance is recommended for CHB patients on antiviral therapy.

In accordance with BCLC classification, early stage HCC can be treated with surgery, hepatic resection being the treatment of choice for no cirrhotic HCC patients, and liver transplantation is recommended for patients with early HCC not suitable for resection (e.g., multifocal small tumors, cirrhosis with severe liver dysfunction). Other effective treatments include local ablation therapy, like radio frequency ablation, used in patients with early-stage HCC who are not suitable for surgical treatment, and transarterial chemoembolization, indicated for intermediate-stage unresectable HCC with no vascular invasion or extra hepatic spread. Radioembolization (internal radiation therapy) using 90Y-labeled glass or resin microspheres is also available in some referral centers for treating unresectable HCC. However, comparative data among these therapies is lacking.

For patients with advanced stage HCC or those who progress after loco-regional therapies, sorafenib is the best available therapy. It is an oral multikinase inhibitor that increases apoptosis and reduces cell proliferation and angiogenesis, approved in 2007 for the treatment of HCC in patients who are not candidates for surgery or local ablation and do not have severe cirrhosis.

Cardoso et al. publish in this issue of GE the experience of 36 HCC Portuguese patients treated with sorafenib and conclude that the main factor of prognosis identified, beyond ChildPugh class and BCLC stage was the occurrence of significant adverse events (AEs).

Several studies on sorafenib also support the observation that the occurrence of clinically relevant AEs (grade $\geq$2 according to NCI-CTCAE scale), especially hypertension, diarrhea and skin lesions[8–12] are associated with higher chances of tumor response and therefore survival improvement.

So, according to some authors, AEs may represent a surrogate of response and be associated with a favorable outcome, encouraging sorafenib continuation rather than its interruption.

In a very recent prospective study[13] seeking to measure the efficacy of a sorafenib dose reduction regimen, adjusted on patient's tolerability, and aimed at increasing the exposure to the drug, the authors concluded that in patients with advanced hepatocellular carcinoma, sorafenib dose adjustments based on inducing tolerability of relevant AEs prolong drug exposure and maximize survival.

The two studies published in this issue of GE underline, as key messages, the importance of HCC surveillance, even in chronic hepatitis B patients on successful antiviral therapy, and the benefits of sorafenib in the treatment of advanced HCC, with the best results being probably obtained in cases with AEs that do not preclude maintenance of therapy.

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