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Review Article

Circulating Tumor Cells Measurements in Hepatocellular Carcinoma

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Liver cancer is the fifth most common cancer in men and the seventh in women. During the past 20 years, the incidence of HCC has tripled while the 5-year survival rate has remained below 12%. The presence of circulating tumor cells (CTC) reflects the aggressiveness nature of a tumor. Many attempts have been made to develop assays that reliably detect and enumerate the CTC during the development of the HCC. In this case, the challenges are (1) there are few markers specific to the HCC (tumor cells versus nontumor cells) and (2) they can be used to quantify the number of CTC in the bloodstream. Another technical challenge consists of finding few CTC mixed with million leukocytes and billion erythrocytes. CTC detection and identification can be used to estimate prognosis and may serve as an early marker to assess antitumor activity of treatment. CTC can also be used to predict progression-free survival and overall survival. CTC are an interesting source of biological information in order to understand dissemination, drug resistance, and treatment-induced cell death. Our aim is to review and analyze the different new methods existing to detect, enumerate, and characterize the CTC in the peripheral circulation of patients with HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is responsible for significant morbidity and mortality in cirrhosis and also accounts for between 85% and 90% of primary liver cancer [1–3]. Most of HCCs in the world occur in the setting of cirrhosis and over half-million of people develop liver cancer every year and an almost equal number die of it [1, 2, 4].

The most important causes leading to HCC are the HBV and HCV infections, heavy alcohol consumption, aflatoxin B1, age and gender (males are more susceptible than females), race (Asian and African over 20 years old), tobacco consumption, obesity associated with nonalcoholic fatty liver disease, and the increase of the Diabetes II mellitus (that rises the risk factor between 2 and 3), genetic hemochromatosis, primary biliary cirrhosis, and alpha1-antitrypsin deficiency and autoimmune hepatitis [1, 2, 5–32].

Usually, HCC develops during a long process of inflammation and fibrosis, eventually leading to cirrhosis [2, 16, 33, 34].

HCC is one of the most aggressive cancers. Patients who show progress over the terminal stage have 1-year survival of less than 10%. The choice of the therapy and the prognosis are dictated by the severity of the liver function, portal hypertension, and medical comorbidities. National and international consensus was established to choose the best treatment adapted for each case and obtain the best prognosis [1, 5–21, 24, 25, 27, 30, 35, 36].

In the field of biology of tumors, some expressions have been coined for the different types of circulating cellular elements. The term *circulating tumor cells* (CTC) defines specifically the tumor cells detected in blood or lymphatic vessels. Circulating cells in the bloodstream or in the lymphatic system are considered to be tumoral microemboli (CTM) and represent a collective migration. The terms disseminated tumor cells (DTCs) and isolated tumor cell (ITC) can be also found in the literature but are usually used to define the cells that can be detected in both the organs and the bloodstream. The word micrometastasis is usually used