SYSTEMATIC REVIEW

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Hepatocellular carcinoma – A review

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Hepatocellular carcinoma is a major public health issue, occupying the fifth place of the most common cancers and the third leading cause of cancer in the world. The incidence of HCC has increased in the past decade thanks to higher rates of HCV infection and improvements in the management of cirrhotic patients. The regions with the highest incidence of HCC are, in descending order: Eastern Asia, sub-Saharan Africa, South-East Asia and southern Europe. It has been observed that etiological factors which lead to HCC have a heterogeneous distribution; thereby, in Asia and Africa the most common risk factor is HBV infection, increased by ingestion of aflatoxin B1-contaminated food that is associated with a specific mutation in the p53 tumor suppressor gene. HCC may develop earlier in these regions, most common in a noncirrhotic liver. In developed countries, the principal risk factors are HCV infection and alcohol-related cirrhosis [1].

RISK FACTORS

The main risk factors involved in the development of HCC are chronic viral infections, hemochromatosis and alcoholic cirrhosis. Other risk factors which may lead to HCC are cirrhosis secondary to autoimmune hepatitis and Wilson disease. In the last years, diabetes was suggested as HCC risk factor in numerous studies. However, it is difficult to study the possible association between the two concepts, because diabetes is a risk factor for nonalcoholic liver disease and nonalcoholic steatohepatitis , which may lead to the appearance of liver fibrosis, of cirrhosis, and finally to HCC, being known the fact that the principal risk factor is the presence of cirrhosis, no matter of the cause. On the other hand, end stage liver disease may herself determine glucose intolerance and diabetes. Studies show that >90% of patients with cirrhosis have glucose intolerance and 30% have diabetes [2].

Cirrhosis is a premalignant statement independent to the etiology. Liver cell dysplasia is probably the intermediate step. Patients with cirrhosis and high rates of cellular proliferation are at high risk to develop hepatocellular carcinoma.

HBV and HVC. It has been shown that there is an interval of 15-40 years between the development of chronic hepatitis and the appearance of hepatocellular carcinoma and the distance is shorter for the virus C infection. For hepatitis B, is important to know the age at which the infection occurred- patients infected in the prenatal period or in childhood are at high risk to develop chronic hepatitis or to become chronic carriers and at the same time to develop cirrhosis and hepatocellular carcinoma.

HBV is responsible for almost 80% of hepatocellular

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carcinoma. Vaccination against HBV and antiviral treatment are the most efficient ways for prevention. HBV seems to be directly and indirectly carcinogenic. There is a connection between the level of replication of virus B (viral load) and the risk of hepatocellular carcinoma. HBV integrates into the genome host and the viral load precedes almost always the development of hepatocellular carcinoma, leading to mutations at the place of integration and high levels of TNF-α. HBx protein inhibit the p53 tumor suppressor gene and activate genes implied in the control of cellular growth. Patients with HB antigen positive infected with delta virus have a reduced incidence of hepatocellular carcinoma, probably because delta virus suppress HBV.

HCV, despite HBV, is an ARN virus which does not have reverse transcriptase and can't integrate into the genome host. The manner of carcinogenesis production is uncertain, but probably is generated by chronic hepatitis and cirrhosis. Persistent hepatitis with high levels of alanine aminotransferase is a semnificative predictor of hepatocellular carcinoma development. Accelerated cellular turnover is implied in the pathogenesis of cirrhosis; at the same time, it has been demonstrated that patients with persistent hepatic injury develops a sort of HCV species that metamorphoses in time, meanwhile patients with normal aminotransferase levels have a stabile infection with a single species of HCV. It seems that during this process are produced species more ,,oncogenic" of HCV core protein. HCV reacts with cellular genes that regulates the cellular growth and differentiation. P53 activity is suppressed and tumor suppressor functions are disabled. HCV core proteins are probably oncogenic [3].

Alcohol intake increases four time the risk of hepatocellular carcinoma development, especially in older patients; cirrhosis is always present. The risk of hepatocellular carcinoma is highest in patients with chronic hepatitis and persistent hepatocellular injury. Patients who stop the alcohol intake reduce considerably the risk of hepatocellular carcinoma development. The enzyme induction mediated by alcohol increases the conversion of co-carcinogens in carcinogens.

Aflatoxin B1, produced by Aspergillus flavus and Aspergillus parasiticus is a pro-carcinogen which is converted in the liver into a metabolite by the cytochrome P450 system at the 8,9-vinyl bond with the formation of an unstable reactive intermediate, aflatoxin B1-8,9-epoxide, which can bind covalently to DNA. The result is the formation of Aflatoxin B1-guanine adducts and protein- aflatoxin B1-albumin and other protein adducts. In addition, aflatoxin B1 acts as a carcinogen by mechanisms that include the formation of reactive oxygen species leading to increased hepatic damage [4].

Sex and genetic predisposition. Globally, hepatocellular carcinoma is 3 times more frequent in males than females. In regions with increased incidence, familial history of hepatocellular carcinoma is an important factor. It is possible to exist a genetic predisposition for hepatocellular carcinoma or a familial predisposition for an extended phase of HBV replication.

Other factors. Hepatocellular carcinoma is a rare complication of autoimmune hepatitis and primary biliary cirrhosis; it may occur frequently in hemochromatosis (in almost 45% of cases, due to excessive levels of free iron submitted in tissues, carcinogenic by the formation of reactive oxygen species). α1-antitrypsin deficiency, tyrosinosis, porphyria cutanea tarda, Clonorchis sinensis infection may also increase the risk of hepatocellular carcinoma development.

There have been identified certain factors which may decrease the risk of HCC in patients with cirrhosis : high serum retinol levels, high coffee consumption, alcohol cessation, clearance of HCV virus with treatment, iron depletion of hemochromatosis patients [5].

PATHOGENESIS

The pathogenesis of HCC is not fully understood, but most probably HCC results from activation of proto-oncogenes, deactivation of tumor suppressor genes (p53, pRb), changes in growth factors signaling processes (insulin-like growth factor-IGF, transforming growth factor-TGF), changes in telomeric length and

activity or microsatellite instability. Genetic injury may result from a variety of sources, such as HBV and HCV viruses. HBV is associated with a relatively high frequency of mutations as it replicates through RNA-mediated reverse transcription and the HBV reverse transcriptase (HBV-RT) does not have proofreading function. Unlike HBV, HCV is a single-stranded non-retroviral RNA virus which does not integrate into the host genome.

Although there have been identified multiple genetic abnormalities in the development of HCC, it is probably that the process is complex and genetic studies are continuing [1].

DIAGNOSIS

Hepatocellular carcinoma should be suspected in patients with previously compensated cirrhosis who develop decompensation, such as encephalopathy, ascites, jaundice or variceal bleeding associated with the extension of the tumor into the hepatic or portal veins or arteriovenous shunt induced by the tumor. Other uncommon presentations include: para-neoplastic syndromes – hypercalcemia (by PTH-like synthesis), erythrocytosis (by EPO-like synthesis), carcinoid syndrome, porphyria cutanea tarda, vascular angioma.

Diarrhea may be the reason for presentation to hospital, caused by cholestasis or the production of prostaglandins by the tumor.

Cutaneous manifestations include pemphigus foliaceus, dermatomyositis, Leser-Trelat sign (suddenly installed seborrheic keratosis, accompanied by freckles, very itchy).

Acute presentation is determined by spontaneous rupture of the tumor into the peritoneum or invasion of the liver capsule. In this case, the preferred treatment is the chemoembolization of the bleeding artery. Capsule invasion is causing severe pain, similar to biliary colic, lasting less than 24 hours.

In end stages, patients may present consumptive syndrome with impaired general condition, anorexia, weight loss and fatigue.

Physical examination can detect an abdominal mass and a bruit related to arterioportal shunting may be heard. A supraclavicular lymphadenopathy (Virchow-Troisier), Sister Mary Joseph or axillar lymph-adenopathies are rarely present [6].

Laboratory studies can show high levels of aminotransferase, but can be also normal. Alkaline phosphatase may be elevated in infiltrative tumor or if there is biliary obstruction due to malignancy. α-fetoprotein, the tumor marker most frequently associated with hepatocellular carcinoma (a glycosylated protein expressed in proliferating hepatocytes) has a sensitivity of 41-65% and specificity of 80-94% when the cut-off value is 20 ng/ml; levels higher than 400 ng/ ml are likely to be caused by hepatocellular carcinoma. AFP>1000 ng/ml associated with a liver mass is diagnostic for hepatocellular carcinoma. However, AFP level is elevated in only 60-70% of patients and false-positive results may occur during pregnancy, in active liver disease, certain gastrointestinal tumors and embryonic tumor. Additional studies of AFP have revealed that AFP has three glycoforms (AFP-L1, AFP-L2, AFP-L3) according to their binding ability to the lectin lents agglutinin (LCA). It has been shown that AFP-L3 exists only in the serum of patients with hepatocellular carcinoma at a cut-off value of 15%, with a sensitivity and specificity of 96.9% and 92%, respectively, in detecting hepatocellular carcinoma [7].

Des-gamma carboxyprothrombin (DCP-prothrombin,a protein induced by vitamin K-absence, PIVK-II) has been described as a protein produced by malignant hepatocytes. Different studies have shown than a combined analysis of AFP and DCP can lead to a better prediction in early stages of hepatocellular carcinoma [8]. Glypican-3, a member of the glypican famlily, has been revealed as a diagnosis marker, having the capacity to differentiate hepatocellular carcinoma from cirrhotic liver or benign lesion. It has been demonstrated that Glypican-3 and AFP together increase sensitivity and specificity for the diagnosis of small and unicentric HCC, respectively [9].

Heat shock protein 70 (HSP) – a protein produced by cells as a response to exposure to stressful conditions, may also be used as a marker for diagnosis in hepatocellular carcinoma [10].

The International Consensus Group of Hepatocellular Neoplasia recommends to define a pathological diagnosis of hepatocellular carcinoma if at least 2 markers are positive.

Imaging diagnosis

A minimum of 2 imaging exploration is required for staging and to confirm/exclude vascular invasion (ultrasound, CT with contrast, MRI); additionally is performed chest CT and bone scintigraphy if taken into account liver transplantation. In case of portal vein thrombosis associated with a small hepatic lesion, Doppler ultrasound is performed and thrombus punction ultrasound guided; the presence of thrombus exclude the possibility of radical treatment. Arterial signal into the thrombus indicate the tumoral etiology.

Abdominal ultrasonography has a 50% sensitivity in hepatocellular carcinoma detection for liver with advanced cirrhosis. Lesions under 2 cm can usually be detected.

Ultrasound appearance is variable. Lesions are usually hypoechoic. In large hepatocellular carcinoma, hyperechoic or heterogenic appearance is due to necrosis, hemorrhage or fat infiltration. Small hepatocellular carcinomas can be homogeneously hyperechoic and can be similar to hemangioma (due to a large portion of fat being present in the tumor) or can appear hypoechoic. Doppler ultrasonography can be used in the detection of portal vein, hepatic artery or inferior vena cava invasion. Portal venous invasion is more common in hepatocellular carcinoma, but hepatic vein invasion is more specific.

Small hyperechoic masses seen on ultrasound require further examination, because they can represent hemangioma (most frequently), metastatic disease or, less likely, hepatocellular carcinoma. Further imaging with CT scanning or MRI during dynamic contrast enhancement shows the typical peripheral, nodular contrast enhancement pattern of hemangioma. MRI or CT scanning can further characterize many nonspecific hepatic masses seen on ultrasonography.

CT scan – dynamic CT, spiral CT is the investigation of election for hepatocellular carcinoma diagnosis. The CT appearance of hepatocellular carcinoma is variable, depending on image phase and tumor size. The most common attenuation pattern is iso-hyper-iso-attenuation on prephase, arterial phase and venous phase, respectively; however, this pattern is common to other hepatocellular nodules, including regenerative and dysplastic nodules.

Unenhanced CT typically shows an iso-hypodense mass; for large masses central areas of necrosis may be seen.

In the hepatic arterial phase, nodules appear hyperdense (relative to hepatic parenchyma), as a result of hepatic arterial supply. Larger tumors may have necrotic central regions that are usually hypodense during this imaging phase. Neovascularity indicate the presence of inconspicuous lesions.

In the portal venous phase, small nodules may appear isodense or hypodense and larger nodules with necrotic regions remain hypodense.

In the delayed-postcontrast phase, small nodules may be inconspicuous on late phases.

Spiral-CT evidentiate 17% of lesions <1 cm, 29% of lesions between 1 and 2 cm and 63% of lesions higher than 2 cm.

MRI has higher sensitivity for focal hepatic lesions than CT.

Precontrast and postcontrast MRI has a 70-85% chance of detecting a solitary mass of HCC.

MRI can differentiate cirrhotic nodules from HCC: if the mass is bright on T2-weighted images, it is HCC until proven otherwise; if the mass is dark on T1- and T2-weighted images, it is a siderotic regenerative nodule or siderotic dysplastic nodule; if the mass is bright on T1-weighted images and dark or isointense on T2-weighted images, it is a dysplastic nodule or low-grade HCC [11].

Hepatic angiography.

Hepatocellular carcinoma is vascularized by hepatic artery and selective arteriography of superior mesenteric artery or celiac artery may identify the lesion. This is an invasive procedure used for hepatic chemoembolisation.

Liver biopsy.

For small lesions detected on ultrasound or CT, histological confirmation is very important. Biopsy is performed with ultrasound or CT guidance. There is a possibility of sowing on the needle path.

In present, the diagnosis of hepatocellular carcinoma is established by clinical examination associated with typical imaging aspect, with/without increased α-fetoprotein, histological confirmation not being absolutely necessary.

EASL 2016 recommend to perform liver biopsy for lesions with atypical imaging aspect and in non-cirrhotic patients [12].

DIFFERENTIAL DIAGNOSIS OF HEPATOCELLULAR CARCINOMA IN THE PRESENCE OF CIRRHOSIS

The major problem consist in the differentiation between hepatocellular carcinoma and a dysplastic nodule. Hepatocellular carcinoma appear hyper-vascularised compared to surrounding tissues.

For lesions higher than 2 cm identified in 2 different imaging studies, in the presence of cirrhosis, the diagnosis of hepatocellular carcinoma can be established. Also, if the lesion is identified in 2 different imaging studies and α-fetoprotein level is higher than 400 ng/ml, the diagnosis is very probable and histological confirmation is not really necessary [1].

SCREENING

Hepatocellular carcinoma screening is recommended in patients at high risk, such as male patients, HBV, HCV viruses, age > 40 years and chronic liver disease, especially cirrhosis and high grade dysplasia.

EASL 2016 clinical practice guidelines on the management of hepatocellular carcinoma recommend screening for patients with chronic HBV infection, even without cirrhosis, Asian males >40 years, females >50 years, patients with family history of hepatocellular carcinoma, African Americans >20 years, primary biliary cirrhosis stage 4, hemochromatosis, α1-antitrypsin deficiency.

Recommended screening methods are abdominal ultrasound combined with α-fetoprotein every 6 months. In cirrhotic patients, a nodule <1 cm detected must be supervised every 4 months for 1 year, than every 6 months.

For nodules 1-2 cm in diameter, the diagnosis is established by non-invasive criteria or histological examination.

Nodules higher than 2 cm may be diagnostic for hepatocellular carcinoma in case of typical aspect; for atypical aspect, histological examination is required [12].

TREATMENT OPTIONS

The treatment is established using the Barcelona-Clinic Liver Cancer (BCLC) staging system which defines very early stage cancer (single nodule,<2 cm, Child-Pugh A) as stage 0, early stage cancer (1-3 nodules, <3 cm each, Child-Pugh A-B) as stage A, intermediate stage for multinodular HCC (stage B), advanced stage which involves vascular invasion or extrahepatic spread (stage C) and terminal stage at patients with Child-Pugh C cirrhosis. Resection, ablation and transplantation is recommended for stage 0 and A, transcatheter arterial chemoembolization for stage B, Sorafenib – stage C and best supportive care for terminal stage.

Surgical treatment

Resection is curative, but limited in patients without cirrhosis or in the presence of cirrhosis and without portal hypertension. It is accepted as treatment for localized hepatocellular carcinomas. Intrahepatic recurrence is common, because the potential of neoplastic liver remain unchanged. The rate of recurrence at 5 years is almost 52 %. Partial hepatectomy is indicated in the absence of cirrhosis or in Child-Pugh stage A with normal portal pressure and normal bilirubin. The best results are obtained in patients with unicentrical disease, without vascular invasion, under 5 cm and with liver disease relatively inactive (5% of hepatocellular carcinomas). 5-year survival rate for curative treatment (resection, transplantation and local ablation therapy) is almost 80%.

Liver transplantation – the technique is successful in

selected patients, but it requires immunosuppressive treatment for life. It is indicated in patients with advanced cirrhosis (Child-Pugh B and C) who cannot survive on surgical resection. Liver transplantation can be applied independently on the liver stage disease and treat both hepatocellular carcinoma and neoplastic potential of cirrhotic liver.

Liver transplantation is indicated for unique tumors under 5 cm or <3 nodules (Milano criteria), each less than 3 cm.

It is difficult to elect between resection and transplantation for a tumor <5 cm. Altered liver function is in favor of transplantation.

Nonsurgical treatment

Chemotherapy

Sorafenib, a Raf-kinase and tyrosine kinase inhibitor, is indicated in patients with normal liver function (Child-Pugh A) and portal vein thrombosis, extrahepatic tumors and failure of other therapies. In patients with altered liver function, only best supportive care is indicated.

Local ablation-is potentially curative in patients with small tumors, <3-5 cm that are not candidates for resection or transplantation.

TACE (Transarterial chemoembolisation) – hepatic artery catheterization via the femoral artery or celiac axis allows the nutrient vessel embolization of tumor, and chemotherapeutic agents can be delivered in high concentrations. (Cisplatinum, Doxorubicim, foam gel, Epirubicin). Chemoembolization is indicated in unresecable tumors, patients with Child-Pugh A-B. The result is partial/total tumoral necrosis. The most frequent side effects are fever, nausea, encephalopathy, ascites and high levels of aminotransferase.

Percutaneous injection of ethanol (PEI) is efficient in 2-3 cm tumors (<5 cm), usually less than 3 nodules, even in the presence of advanced cirrhosis. The technique suppose the ethanol injection under ultrasound/CT guidance; outpatient treatment may be carried out 2 times per week, 3-15 sessions, using 2-16 ml of absolute alcohol. 3-year survival rate is 71% in patients with Child-Pugh A and 41% in Child-Pugh B.

Radiofrequency ablation (RFA) is a treatment that uses imaging guidance to place a needle electrode through the skin into a liver tumor. High-frequency electrical currents are passed through the electrode, creating heat that destroys the cancer cells. RFA is more effective than PEI in larger tumors (3-5 cm) and it requires fewer sessions. Recurrence rates are higher than in resection, but survival rate is similar to resection.

Trans-catheter arterial chemoembolization uses angiography and allows the nutrient vessel embolization of tumor. TACE is recommended in palliative treatment for unresecable tumors and in patients on transplantation list; the effectiveness of the method depends on the tumor dimension. TACE it is not recommended in the treatment of large and unresecable tumors.

CONCLUSION

In conclusion, hepatocellular carcinoma remain a fatal disease. All treatments used increases survival. Some studies have shown that there were no big differences between the results given by resection, transplantation and arterial embolization [13].

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