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Hepatocellular Carcinoma: A Focus on the New Lines of Management

Ahmed M. Kabel[1,2,*], Abrar A. Al-joaid[3], Afnan A. Al-ghamdi[3], Aseel A. Al-joaid[3], Wejdan S. Al-zaidi[3]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, KSA
[2]Department of Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt
[3]Final year student, College of Pharmacy, Taif University, Taif, KSA
*Corresponding author: drakabel@gmail.com

Abstract Hepatocellular carcinomas (HCCs) are aggressive tumors with a high dissemination rate. Diagnosis of HCC depends on physical examination, computed tomography, magnetic resonance imaging and biopsy results. An early diagnosis of these tumors is of great importance in order to offer the possibility of curative treatment. HCC is relatively insensitive to systemic therapy, radiotherapy or surgery and this usually depends on the stage of the disease. Diagnosis and treatment of HCC has witnessed many major changes and challenges in the past years. New alternative lines of treatment of HCC were developed to attack the tumor at the molecular level to improve the prognosis and achieve better results. These include check-point inhibitor therapy, molecular targeted therapy and angiogenesis inhibitors.

Keywords: *hepatocellular, cancer, pathogenesis, diagnosis, management*

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1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent hepatic malignancy and accounts for as many as 1 million deaths per year worldwide. In some parts of the world, it is the most common form of internal malignancy and the most common cause of death from cancer [1]. It is less common in most parts of the developed Western world but appears to be increasing in incidence. Because it usually occurs as a complication of chronic liver disease, the diagnosis of HCC is often made by gastroenterologists and hepatologists, who are also becoming more involved in the management of patients with this form of cancer [2].

Hepatocellular Carcinoma (HCC) is the most common type of primary liver cancer, followed by cholangiocarcinoma. It represents the main complication of liver cirrhosis, and shows a growing incidence worldwide related to the increased prevalence of the various risk factors of chronic liver diseases, such as infection with hepatitis C and B viruses, and fatty liver diseases which are mostly associated with metabolic syndrome [3].

2. Risk Factors for the Development of HCC

Patients at high risk for developing HCC include those with cirrhosis secondary to hepatitis B and C viruses, alcohol ingestion, genetic hemochromatosis, autoimmune hepatitis, steatohepatitis, primary biliary cirrhosis and alpha 1-antitrypsin deficiency. Patients at risk without cirrhosis include hepatitis B carriers and those with non-alcoholic steatohepatitis. Groups at high risk should be entered into surveillance programmes by experienced personnel using abdominal ultrasound every 6-12 months and alpha fetoprotein levels [4].

Although most HCC develop in the background of chronic liver disease, some may occur in normal liver and usually correspond to specific types, including fibrolamellar HCC mostly encountered in young population, or malignant transformation of hepatocellular adenomas. Overall, HCC is associated with poor prognosis depending on delayed diagnosis, the clinical status of the patient and the high possibility of distant metastasis [5].

3. Pathophysiology of HCC

The pathologic changes including inflammation, necrosis, fibrosis and regeneration that characterize the cirrhotic liver often contribute to HCC development. The diseases that result in malignant transformation include a variety of pathways that may be modified by external and environmental factors leading to genetic changes that delay apoptosis and increase cellular proliferation [6].

Many genetic pathways may be altered during hepatocarcinogenesis. Among these pathways, the p53 and β-catenin genes appear to be the most frequently mutated in patients with HCC. Two pathways involved in cellular differentiation (*Wnt-β-catenin*, *Hedgehog*) appear to be frequently altered in HCC. Upregulated WNT signaling appears to be associated with preneoplastic adenomas with

a higher rate of malignant transformation [7]. Additionally, studies of inactivated mutations of the chromatin remodeling gene ARID2 in the major subtypes of HCC are being performed. Their results suggest that ARID2 is a tumor suppressor gene commonly mutated in this tumor subtype [8].

Prospective studies suggest that the presence of small-cell dysplastic nodules conveyed an increased risk of HCC while large-cell dysplastic nodules were not associated with an increased risk of HCC. Evidence linking small-cell dysplastic nodules to HCC includes the presence of conserved proliferation markers and the presence of nodule-in-nodule on pathologic evaluation. This term describes the presence of a focus of HCC in a larger nodule of small dysplastic cells [9].

Some investigators suggested that HCC develops from hepatic stem cells that proliferate in response to chronic regeneration caused by viral injury. The cells in small dysplastic nodules appear to carry markers consistent with stem cells [10].

Three gross morphological types of HCC have been identified. The nodular type is often associated with cirrhosis, characterized by well-circumscribed nodules. The massive type is usually associated with non-cirrhotic liver, occupies a large area with or without satellite nodules in the surrounding liver. The diffuse type is less common. Diffuse involvement of many small indistinct tumor nodules throughout the liver often occurs [11].

4. Clinical Presentation of HCC

Clinical signs and symptoms of HCC are variable depending on tumor size, vascular invasion, the presence of cirrhosis and occurence of metastasis [12]. They include right upper quadrant pain and weight loss. Other signs include worsening liver function in a patient known to have cirrhosis, acute abdominal pain from rupture of a liver tumor with intra-abdominal bleeding, and some rare extrahepatic manifestations. Moreover, patients may be diagnosed with HCC at an asymptomatic stage while they are being evaluated for liver transplantation or as a part of routine screening in those with cirrhosis. Other symptoms include malaise, fever, ascites, jaundice, anorexia and weight loss [13].

5. Diagnosis of HCC

A focal lesion in the liver of a patient with cirrhosis is highly suggestive of HCC. Initial assessment should be by spiral computed tomography (CT) of the liver and thorax. Magnetic resonance imaging (MRI) with contrast enhancement or angiography with lipiodol injection and follow up CT may increase the accuracy of detection of other liver lesions. Biopsy is rarely required for diagnosis, and seeding of tumor in the needle tract may occur in 1–3% of cases. Biopsy of potentially operable lesions should be avoided where possible [14].

6. Classification of HCC

The first classification of HCC was developed in 1985 by Okuda et al. in a study on 850 patients with HCC using data concerning tumor size (> or < than 50% of the liver size), serum bilirubin levels (> ou <3 mg/dl), serum albumin levels (> or <3 g/dl) [15].

Barcelona Clinic Liver Cancer (BCLC) group classification takes into consideration hepatic function, portal hypertension, serum bilirubin, symptoms related to the tumor, tumor morphology, presence of distant metastasis or vascular invasion. This is the only classification that correlates prognostic data with therapeutic possibilities [16].

TNM classification considers the size and number of nodules, vascular invasion and bilobar involvement. Hepatic function is not considered as a factor in staging, although it is an important factor for the prognosis of the patients. Evaluation of this classification in patients submitted to liver transplantation did not show benefits in prognostic terms for patients with HCC. The inclusion of the hepatic fibrosis factor in staging by TNM has been recently suggested [17].

Chinese University Prognostic Index includes the TNM classification associated with serum levels of bilirubin, alkaline phosphatase, AFP, presence of ascites, and absence of clinical symptoms at the time of diagnosis [18]. French classification includes prognostic factors such as the Karnofsky index, serum bilirubin levels, AFP, alkaline phosphatase, and the presence of portal thrombosis detected by ultrasound [17].

7. Prevention of HCC

The most effective method to reduce the worldwide burden of liver cancer is to prevent it from happening in the first place. Some scientists believe that vaccinations and improved treatments for hepatitis could prevent about half of liver cancer cases worldwide. Researchers are studying ways to prevent or treat hepatitis infections before they cause liver cancers. Research into developing a vaccine to prevent hepatitis C is ongoing. Progress is also being made in treating chronic hepatitis [19].

8. Management of HCC

The management of hepatocellular carcinoma depends on a variety of factors including the size, number and distribution of tumors, the relationship of the tumor to hepatic vasculature, the status of distant metastasis, the severity of liver disease, the suitability of the patient for liver transplantation and the functional status of the patient. Hepatocellular carcinoma is relatively insensitive to systemic chemotherapy or radiotherapy and surgery carries poor prognosis [20].

8.1. Surgery

Surgery is the treatment of choice in non-cirrhotic patients with HCC and in cirrhotic patients with well-preserved synthetic functions. However, only 20% of patients are potentially resectable at the time of presentation. In non-cirrhotic patients, surgical mortality is less than 3% in experienced hands, but increases to 8% in patients with cirrhosis. The overall 5-year survival rate after surgical resection is 35-45% for small tumors [21,22].

8.1.1. Hepatic Resection

Surgical resection is considered to be the treatment of choice for patients with HCC. However, due to the frequent occurrence of postoperative hepatic decompensation, this treatment modality should be indicated only for patients with preserved hepatic function. Non-judicious patient selection for surgical resection may not lead to increased survival when surgical treatment is compared to the natural history of HCC or even to other less invasive therapies [23].

8.1.2. Liver Transplantation

Liver transplantation is the treatment of choice in cases of HCC limited to the liver and cannot be submitted to surgical resection due to poor hepatic function or to technical difficulties. Liver transplantation not only eliminates the neoplasia, but can also cure the basic liver disease. Some authors adopt post-resection tumor recurrence as an indication for liver transplantation. Others adopt liver transplantation as the treatment of choice before resection. When strict selection criteria are used, such as a single, small tumor (<5 cm) without satellite nodules, without vascular invasion, without invasion of regional lymph nodes, without distant metastasis and without an indication for resection, a satisfactory survival can be obtained [24].

8.1.3. Cryosurgery (Cryotherapy)

This procedure destroys a tumor by freezing it using a thin metal probe. The probe is ultrasound-guided into the tumor and then very cold gases are passed through the probe to freeze the tumor, killing the cancer cells. This method may be used to treat larger tumors than the other ablation techniques, but it sometimes requires general anesthesia. It is safe and efficacious in the treatment of unresectable and recurrent HCC [25].

8.2. Locoregional Therapy

All hepatocellular carcinoma patients should be evaluated for potential curative therapies (resection, transplantation). The patients not candidates for curative treatments may be treated with locoregional approaches such as transarterial embolization and ablative therapy [26].

8.2.1. Transarterial Embolization or Chemoembolization

Since HCC is a tumor predominantly irrigated by the arterial system of the liver, blockade of the blood supply to the tumor is used as treatment. Tumors that cannot be submitted to radical treatment are considered for transarterial embolization (TAE)/ chemoembolization (TACE). TAE consists of gelatin sponge particles, polyvinyl alcohol particles, and polyacrylamide microspheres. TACE is distinguished from TAE by the catheter-based administration of a concentrated dose of chemotherapy [27].

8.2.2. Ablative Therapy

Percutaneous local ablation techniques are currently considered as the best treatment option for patients with early-stage HCC who are not candidates for surgical resection. They are safe, minimally invasive, efficacious and cost-effective. Radiofrequency ablation is considered as the first line treatment in some centers, though most of the guidelines recommend it for small HCCs, where surgical resection is not feasible. Percutaneous ablative therapies are well described, most commonly using ethanol or acetic acid injection (Ultrasound-guided). Cisplatin gel infusion (Percutaneous cispatin gel infusion) is a new and promising therapeutic option for the treatment of unresectable and recurrent liver tumors [28].

8.3. Radiation Therapy

Radiation therapy uses high-energy rays to kill cancer cells. There are different kinds of radiation therapy.

8.3.1. External Beam Radiation Therapy

This type of radiation therapy focuses radiation delivered from outside the body on the cancer. This can sometimes be used to shrink liver tumors to relieve symptoms such as pain, but it is not used as often as other local treatments such as ablation or embolization. Although liver cancer cells are sensitive to radiation, this treatment can't be used at very high doses because normal liver tissue is also easily damaged by radiation [29].

8.3.2. Radioembolization

This technique combines embolization with radiation therapy and is sometimes known as trans-arterial radioembolization (or TARE). Recently, TARE has given promising results in treatment of patients with intermediate or advanced stage HCC, both in terms of disease control and tolerability profile. This technique consists of the selective intra-arterial administration of microspheres loaded with a radioactive compound and exerts its therapeutic effect through the radiation carried by these microspheres. TARE is a technically complex and expensive technique. However, it may represent an alternative to transarterial chemoembolization (TACE) in treatment of intermediate-stage HCC patients, as shown by a comparative retrospective assessment that reported a longer time to progression, but not of overall survival, and a more favorable safety profile for radioembolization. In addition, this treatment has reported a higher percentage of tumor shrinkage, if compared to TACE, and it represents a promising therapeutic option in patients with large extent of disease and insufficient residual liver volume who are not immediately eligible for surgery [30].

8.3.3. Radiofrequency Ablation

Radiofrequency ablation (RFA) is a new technique that makes use of a “heating” probe to destroy tumors within the liver. A thin probe is placed within the tumor, typically under ultrasound guidance. After deploying the tip array, an electrical current is applied, generating heat (80–100°C) that destroys the tumor [31].

8.3.4. Stereotactic Body Radiation Therapy (SBRT)

SBRT is a technique that allows treatment to be completed in a short-time. Radiation therapy usually means getting small doses of radiation 5 days a week for several weeks, SBRT uses very focused beams of high-dose radiation given on one or a few days. Beams are aimed at the tumor from many different angles. To target the radiation precisely, the person is put in a specially

designed body frame for each treatment. Although the indications for SBRT for HCC have evolved, the role of SBRT in HCC is less clear. Future studies should focus not only on maximizing efficacy, but also on determining how SBRT should be used in the context of other previously established therapies. Careful patient selection is required and SBRT should be considered only after thorough discussion with all legitimate treatment options also considered [32].

8.4. Systemic Therapy

Systemic therapy uses medications to treat cancer cells throughout the body. Systemic treatments include chemotherapy, immune therapy and hormonal therapy.

8.4.1. Chemotherapy

8.4.1.1. Overview of Chemotherapy of HCC

Chemotherapy is generally considered for use in patients with HCC not amenable to other lines of treatment such as surgical resection, transplantation, or ablation, and therefore its role is largely palliative. Varieties of chemotherapeutic agents have been tested against HCC. Few reliably are associated with antitumor responses. Chemotherapy may be administered either systemically or regionally [33].

Regional chemotherapy includes intra-arterial treatment, the results of which are similar to chemoembolization. Systemic chemotherapy is associated with low response rates (typically less than 25% objective responses) and dosing may be limited by cirrhosis often associated with HCC. Antiangiogenic agents hold considerable promise in the treatment of HCC because of the vascularity of this tumor. Thalidomide is an agent with both antiangiogenic and immunomodulatory actions that has proven efficacy in patients with HCC [34].

8.4.1.2. Molecular Targeted Therapy of HCC

The pathways that affect hepatic carcinogenesis include many growth factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor and regulating specific intracellular pathway (RAF/MEK/ERK pathway) [35]. For example, the activation of the RAF/MEK/ERK pathway may lead to the growth of HCC. The EGF may bind to its receptor and trigger signal transduction through the RAF/MEK/ERK pathway. Moreover, VEGF may result in angiogenesis and HGF will bind to the c-MET receptor and other molecular signal pathways, including PI3K/PTEN/Akt/mammalian target of rapamycin (mTOR) pathway. Recently, many studies have focused on targeted molecular agents and tried to block one or more steps in carcinogenic pathways for inhibition of tumor formation [36].

Sorafenib has been introduced for patients with advanced HCC. Sorafenib belongs to the multi-targeted tyrosine kinase inhibitors and anti-angiogenic agents. It may inhibit abnormal growth of multiple cell surfaces and intra-cellular kinases which would be involved in angiogenesis, cell proliferation and differentiation. Moreover, sorafenib was shown to inhibit the RAF/MEK/ERK pathway. Sorafenib showed a statistically significant improvement in the survival rate in advanced HCC and is considered to be a standard therapy as it inhibits growth and angiogenesis of HCC [37].

Although sorafenib is the first and only targeted therapy approved for advanced HCC, it has been studied in combination with other systemic chemotherapeutic agents such as doxorubicin [38]. The combination of doxorubicin and sorafenib improved the median survival rate compared to doxorubicin alone. However, the effects and mechanisms of doxorubicin in this synergism still remained unclear. Also, sorafenib was combined with other systemic agents, such as octreotide with encouraging results [39]. All of these trials reported improved OS when compared to sorafenib alone; however, the sample sizes were small. The exact and final outcomes deserve intervention. However, resistance to sorafenib may develop, possibly due to the genetic heterogeneity and activation of the compensatory pathways, such as the PI3K/Akt and JAK-STAT pathways or tumor hypoxia [35].

A variety of other multiple tyrosine kinase inhibitors has been recently developed after the impact of sorafenib. Sunitinib was proved to inhibit the VEGFR, KIT, RET and the fms-like tyrosine kinase-3 receptor. Some of these factors pay a role in both tumor angiogenesis and proliferation. Most of the side effects of sunitinib are very mild, including fatigue, diarrhea, nausea and anorexia [40]. Linifanib is a multi-kinase inhibitor targeting VEGFR and PDGFR. In a phase II trial involving 44 patients (of which 89% were Asian), the single agent linifanib was found to be clinically active in patients with advanced HCC, with an acceptable safety profile [41]. Brivanib is a selective dual receptor inhibitor against fibroblastic growth factor receptor and VEGFR. It was shown to have antitumor activity in patients with advanced HCC in phase II studies [42].

8.4.2. Hormonal Therapy

Hormonal manipulation with tamoxifen has been the subject of randomised clinical trials. Initial data suggesting a positive effect on survival in patients with inoperable HCC has not been confirmed in larger randomised studies [43]. Other agents with hormonal targets, stilbestrol, and flutamide have been used in HCC but there is no evidence of effectiveness. Some authors have suggested that hormonal manipulation may be effective where the oestrogen receptor status is known [44].

8.4.3. The Role of Immunotherapy and Immune Checkpoint Inhibitors in HCC

The inherent immune tolerance of the liver hinders immune surveillance and therefore makes the carcinogenesis of HCC possible. Liver confronts abundant xenogenous antigens within blood from the gut via the portal vein. Specific mechanisms with regards to immune tolerance are activated to inhibit unneeded immune responses. While HCC is not generally considered an “immunogenic” tumor, patients whose tumors contain lymphocytic infiltrates show longer survival and lower risk of recurrence. In the past years, several tumor-associated antigens for HCC have been identified, and a measure of success has been achieved in early clinical trials. The goal of immune-based therapies is to strengthen the sensitivity,

specificity and self-regulation of the immune system to eradicate any tumor foci [45].

Immune checkpoints are molecules in the immune system that either turn up a signal (co-stimulatory molecules) or turn down a signal. Many cancers including HCC may protect themselves from the immune system by inhibiting the T-cell signal. Recently, inhibitory checkpoint molecules have been increasingly considered as new targets for cancer immunotherapy [46]. Checkpoint therapy can block inhibitory checkpoints, restoring immune system function. One ligand-receptor interaction under investigation is the interaction between the transmembrane programmed cell death 1 protein (PDCD1, PD-1; also known as CD279) and its ligand, PD-1 ligand 1 (PD-L1, CD274). PD-L1 on the cell surface binds to PD1 on an immune cell surface, which inhibits immune cell activity [47]. PD-L1 functions as a key regulator on T-cell activities. It appears that cancer-mediated upregulation of PD-L1 on the cell surface may inhibit T-cells that might otherwise attack. Antibodies that bind to either PD-1 or PD-L1 and therefore block the interaction may allow the T-cells to attack the tumor [46]. The first checkpoint antibody approved by the FDA was ipilimumab, which was approved in 2011 for treatment of melanoma. It blocks inhibitory immune checkpoint CTLA-4 [48]. PD-1 inhibitors such as nivolumab and pembrolizumab were approved by FDA to treat melanoma and lung cancer and are under trial for management of HCC [49]. Also, PD-L1 inhibitors such as atezolizumab and avelumab are under trial for management of HCC with promising results [46].

9. Prognosis of HCC

The overall prognosis for patients diagnosed with HCC in the United States is poor, with an estimated median survival of 4.3 to 20 months and a 5-year survival of 10 to 15%. In general, patients who have HCC detected after the onset of symptoms have an extremely poor prognosis, with an overall 5-year survival of 0 to 10%. Symptoms may include abdominal pain, anorexia, early satiety, weight loss, obstructive jaundice, fever, watery diarrhea and bone pain (from metastasis). A selected group of patients with good performance status who have HCC diagnosed at an early stage have a predicted survival longer than 5 years, but unfortunately most patients with HCC have advanced stages of cancer at the time of diagnosis [43].

10. Conclusion

HCCs are aggressive tumors with a high dissemination power. An early diagnosis of these tumors is of great importance in order to offer the possibility of curative treatment. Therapy may help to slow the disease, but these cancers are usually very hard to treat.

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