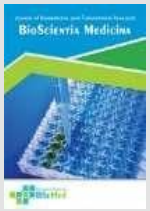
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Diagnosis and Current Management of Hepatocellular Carcinoma

Rivo Armanda Satria[1*], Saptino Miro[2]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Gastroenterology and Hepatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
HCC
Hepatocellular carcinoma
Immunotherapy
TACE
Targeted therapy

***Corresponding author:**
Rivo Armanda Satria

E-mail address:
rivoarmanda@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i3.945

A B S T R A C T

Hepatocellular carcinoma (HCC) is a primary malignant liver tumor originating from hepatocytes which has a very poor prognosis and is ranked the sixth most common cancer disease in the world and is ranked third in deaths caused by cancer worldwide. Symptoms of underlying liver diseases such as hepatitis and cirrhosis often disguise the diagnosis of HCC so that most cases are discovered at an advanced stage. The examination modalities commonly used in surveillance are liver ultrasound (USG) examination and measurement of alpha levels fetoprotein (AFP) with sensitivity diagnostic up to 90%. Non-invasive imaging plays an important role in objective recognition and staging enforcement diagnosis as early as possible so that the patient's prognosis is better. Treatment for early-stage HCC can be given through curative therapy such as resection, liver transplantation, and local ablation, but disease at an advanced stage causes limited options in management where governance The current focus is on systemic therapy with a focus on a combination strategy of immunotherapy or a combination of targeted therapy with immunotherapy as the first line.

1. Introduction

Hepatocellular carcinoma (HCC) is a primary malignant liver tumor that originates from hepatocytes, the same as fibrolamellar carcinoma and hepatoblastoma. Hepatocellular carcinoma is a cancer with a very poor prognosis, with an overall mortality and incidence ratio reaching 95%, and is the third highest cause of cancer death worldwide.[1,2,5] Hepatocellular carcinoma ranks as the sixth most common cancer incidence in the world, with an incidence of 4.7% of 19.3 million cancer cases based on GLOBOCAN data in 2020, HCC is ranked third or 8.3% of the 9.9 million deaths caused by cancer worldwide. The incidence of liver cancer in Indonesia ranks second after lung cancer, at 12.4 per 100,000 population, with an average of 7.6 deaths per 100,000 population. The prevalence is greater in men and is often found in patients suffering from hepatitis B, hepatitis C, chronic liver disease, and liver cirrhosis.[2,3,5,11]

Symptoms resulting from underlying liver diseases such as hepatitis and cirrhosis often mask the diagnosis of hepatocellular carcinoma, making it difficult to recognize the symptoms of this disease at an early stage, so most cases of HCC are found at an advanced stage.[1,3,8,10] The examination modality that is often used in surveillance is examination ultrasonography (USG) liver and measurement of levels of alpha-fetoprotein (AFP) blood, which a combination of these tests can increase sensitivity

diagnostic up to 90% and is also very effective if carried out at intervals every six months, but this also results in a large cost burden. In Indonesia, examinations are recommended for HCC surveillance in populations high risk with ultrasound and AFP and/or PIVKA II (protein-induced vitamin K absence or antagonist-II) every six months.[1,3,5,12]

Examination with non-invasive imaging plays an important role in recognizing and determining the stage of liver tumors with the aim of getting a diagnosis as early as possible at an early stage so that the patient's prognosis becomes better. Imaging examination using ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) is an imaging modality that can be used in the diagnosis of liver tumors.[1,5,7] Management of early-stage HCC can be done with curative therapy such as resection, liver transplantation, and local ablation however, in patients with advanced stages, this causes limited options in the management of HCC where governance The latest focus is on systemic therapy, which has been developed since 2007 until now with a priority on advanced stage HCC with a focus on a combination strategy of immunotherapy or a combination of targeted therapy with immunotherapy as the first line.[1,5,6,14] The high incidence, atypical symptoms at an early stage, and poor prognosis are challenges for health workers, especially internists, to know and understand diagnosis correctly as early as possible so as to provide adequate therapy for the management of hepatocellular carcinoma.

Anatomy, physiology and histology of the liver

The liver is the largest gland in the human body, located in the upper right quadrant of the abdomen, where, under normal conditions, the liver is dark red because it is rich in blood supply. The liver is divided into four lobes, namely the right lobe, caudate lobe, sinistra lobe, and quadratus lobe, and 8 segments based on the flow of blood vessels and bile ducts in each segment. Microscopically, in the human liver, there are 50,000-100,000 lobules, each hexagonal lobule consisting of cube-shaped liver cells arranged radially around the central vein. Between the sheets of liver cells, there are capillaries called sinusoids, which are branches of the portal vein and hepatic artery. The sinusoids are lined by phagocytic cells (Kupffer cells), which are the reticuloendothelial system and function to destroy bacteria and other foreign objects in the body, which makes the liver one of the body's defense organs against attacks by bacteria and toxic substances.[1] Apart from the branches of the portal vein and hepatic artery, which surround the peripheral part of the liver lobules, there are also bile ducts that form bile capillaries called bile canaliculi, which run between the sheets of liver cells.[1]

The liver has various functions, and the main function is the formation and excretion of bile. The liver excretes up to 1 liter of bile per day into the small intestine, where the bile pigment produced is the final product of metabolism and physiologically does not have an active role but is important as an indicator of liver and bile duct disease. Apart from that, the liver's function is also known to store the metabolic results of monosaccharides from the small intestine in the form of glycogen. In protein metabolism, the liver plays a role in producing plasma protein in the form of albumin, which is needed to maintain colloid osmotic pressure, and produces prothrombin, fibrinogen, and other clotting factors. The liver also has a role in fat metabolism, produces lipoproteins, cholesterol, phospholipids, and acetoacetic acid, and plays a role in the detoxification process.[1]

The liver consists of various cells where hepatocytes cover 60% of the liver cells, and the rest consists of epithelial cells of the biliary system and non-parenchymal cells such as endothelium, Kupffer cells, and stellate cells. The cells that are also found in the sinusoid walls are Kupffer phagocytic cells, which are an important part of the reticuloendothelial system, and stellate cells (Ito cells, lipocytes, or pericytes), which have myofibroblastic activity which can help regulate sinusoidal blood flow as well as being an important factor in repairing liver damage. Increased activity of stellate cells is a key factor in liver fibrosis.[1]

Diagnosis and current management of hepatocellular carcinoma

Diagnosis of hepatocellular carcinoma

The diagnostic criteria for HCC are determined based on three factors, namely, background of chronic liver disease, tumor markers, and imaging examination. In the presence of liver cirrhosis, hepatitis B, or chronic hepatitis C, as well as increased levels of tumor markers and typical features on imaging examinations, a definite diagnosis of HCC can be made.[5,8,14]

Table 1. Criteria for diagnosis of hepatocellular carcinoma according to PPHI 2017.[5]

Underlying liver disease (one positive factor) Hepatitis B-related liver disease Hepatitis C-related liver disease Liver cirrhosis
Tumor markers (one of the tests is positive) AFP ≥ 200 ng/mL and tends to increase PIVKA-II ≥ 40 mAU/mL
Typical radiological appearance Hypervascularity in the arterial phase and washout in the portal venous phase or phase delayed on CT examination scan or three-phase MRI
A+B+C or A+C or B+C: The diagnosis of HCC can be made. A+B or B only: HCC is very suspicious, so a CT examination is needed for a scan or three-phase MRI. C only: continue with liver biopsy. If a nodule with an atypical appearance is found, especially a hypervascular nodule without washout in the portal venous phase or hypovascular nodules in the arterial phase, the patient must undergo further examination.

In conditions where the nodule does not give a typical HCC appearance on a CT scan or three-phase MRI, or in nodules with a typical HCC appearance but not accompanied by liver cirrhosis, further examination in the form of a biopsy is needed core or MRI examination with contrast (Gd-EOB-DTPA)/gadoxetic acid which is specific for hepatobiliary or contrast-enhanced ultrasonography (CEUS).[5,7] Pathologic examination is recommended for all nodules occurring in non-cirrhotic livers and nodules in cirrhotic livers that present atypical or inconclusive imaging findings that are associated with a benign regenerative nodule (large regenerative nodule, benign hepatocellular tumor (liver cell adenoma, focal nodular hyperplasia), low-grade dysplastic nodules (LGDN), and high-grade dysplastic nodule. Nodule biopsy is performed by FNA or biopsy core. The advantage of core biopsy is that the sample obtained is tissue with histopathological examination that can assess tissue architecture and describe the transformation between non-tumor tissue and tumor, so core biopsy examination is highly recommended.[5]

In situations where the histopathological examination is doubtful due to the possibility of high-grade dysplastic nodules (HGDN), immunohistochemical panel examination may be recommended glypican-3 (GPC-3), heat shock protein 70 (HSP70) and glutamine synthetase (GS).[5] Histological diagnosis is necessary when there are no contraindications (for lesions > 2 cm in diameter), and a definitive diagnosis is necessary to determine the choice of therapy. In tumors less than 2 cm in diameter, non-invasive diagnosis is difficult because of the high risk of false positives due to immature arterial

vascularization in the nodule. If imaging and biopsy do not provide a definitive diagnosis, it should be followed up with serial imaging examinations every 3 months until a diagnosis can be made.[5,8]

Current management of hepatocellular carcinoma

The staging system basically plays an important role in helping guide the choice of treatment modalities for HCC patients. There are many staging systems that can be used for HCC patients, but currently, the most effective and widely used system is the classification system Barcelona Clinic Liver Cancer (BCLC), which was also adopted by PPHI. The BCLC system can help classify early-stage HCC patients who can still receive curative therapy and advanced-stage HCC patients who only need palliative therapy; however, in the 2021 PPHI consensus, they do not adopt this system in their therapeutic strategy because HCC is heterogeneous.[5,6,8,11]

In the national consensus on systemic therapy for liver cell carcinoma PPHI 2021 in the management of HCC, a management algorithm was adopted from the Asian Pacific Association for the Study of the Liver (APASL) with slight modifications that are different from the previous algorithm. This is because HCC is heterogeneous, where at the same stage, especially the BCLC B stage, it can have a different prognosis and response to therapy and depends on the number of nodules, nodule size, and degree of liver function.[6,8]

"Good liver function" means Child-Pugh A, without ascites or other disorders that could prevent optimal outcomes. Good liver function is necessary to achieve optimal therapeutic outcomes. Performance status (PS) refers to changes in daily functional capacity caused by the presence of a tumor assessed by a doctor based on the classification Eastern Cooperative Oncology Group (ECOG).[5,6]

Current treatment of HCC is still unsatisfactory, where most cases are based on liver cirrhosis. HCC patients with liver cirrhosis have poor tolerance to surgery segmentectomy. Apart from surgery, there are several other modalities such as liver transplantation, chemotherapy, intra-arterial embolization, and tumor injection with ethanol to cause tumor necrosis, but the results of these procedures are still unsatisfactory with a very low 5-year life expectancy.[5,6,14]

HCC therapy modalities include curative therapy and palliative therapy. Potentially curative therapies include resection, liver transplantation, and ablation. Palliative therapy is transarterial chemoembolization (TACE), stereotactic body radiation therapy (SBRT), external beam radiation therapy (EBRT), selective internal radiation therapy (SIRT), and systemic therapy. The choice of HCC therapy modality is determined based on the degree of liver function, performance status, and tumor burden, which includes extrahepatic spread, vascular invasion, number of nodules, and nodule size.[5,6,14]

Liver transplant

In HCC patients with liver cirrhosis, liver transplantation provides the possibility of removing the tumor and replacing the dysfunctional liver parenchyma, but post-transplant death often occurs due to tumor recurrence. Tumor recurrence may even be enhanced by the anti-rejection drugs that must be administered post-transplant. Based on research, tumors with a diameter of less than 3 cm recur less frequently than tumors with a diameter of more than 5 cm, making it an effective therapy for early-stage HCC suffering from advanced liver cirrhosis (Child-Pugh B or C).[1,5,6]

The criteria used for selecting patients for liver transplantation are the Milan criteria, where HCC patients have Child-Pugh C liver cirrhosis with a solitary nodule measuring less than 5 cm or up to 3 nodules measuring less than 3 cm each without any signs of invasion. venous or radiologically distant metastases. These criteria are also recommended in Indonesia, but currently, liver transplantation is not yet a routine procedure for treating HCC.[5,6]

Hepatic resection

Resection is the first line of therapy in patients with solitary tumors who have an optimal profile based on the BCLC system, are not accompanied by cirrhosis,

and have good liver function. However, for cirrhosis patients, selection criteria are needed because surgery can trigger liver failure, which can reduce life expectancy. Parameters that can be used are Child-Pugh score and degree of portal hypertension or serum bilirubin level and degree of portal hypertension only. Patients with normal bilirubin levels without significant portal hypertension have a 5-year life expectancy of up to 70%. Contraindications to this procedure are the presence of extrahepatic metastases, diffuse or multifocal liver cancer, advanced cirrhosis, and comorbidities that may affect the patient's survival during surgery.[5,8,9]

In multifocal tumors, resection can still be considered in patients with a maximum of three nodules and only involving up to three adjacent liver segments, and to date, neoadjuvant therapy or adjuvant therapy has not been proven to improve the outcome of patients with resection or local ablation.[5]

Percutaneous tumor ablation

Destruction of neoplastic cells can be achieved with chemicals (alcohol, acetic acid) or by modifying the temperature (radiofrequency, microwave, laser, cryoablation). Percutaneous ethanol injection (PEI) is the technique of choice for small tumors due to its high efficacy, low side effects, and relative cheapness. The working principle of percutaneous tumor ablation is to cause dehydration, necrosis, vascular occlusion, and fibrosis. In small tumors (< 5 cm in diameter) accompanied by Child-Pugh A cirrhosis, the 5-year survival rate can reach 50%. Percutaneous ethanol injection (PEI) is useful for patients with small tumors whose resectability is limited due to the presence of non-child liver cirrhosis.[5,8]

Another ablation procedure that can be performed is ablation using radio frequency waves. Radiofrequency ablation (RFA) shows a higher success rate than PEI and the highest efficacy for tumors larger than 3 cm but still has no effect on patient survival. In addition, RFA is more expensive and has more side effects compared to PEI. Furthermore, in an effort to prevent recurrence, administration of polyprenoic acid (polyprenoic acid) for 12 months was reported to significantly reduce the recurrence rate at 38 months compared with the placebo group (placebo group 49%, PEI therapy or curative resection group 22%).[5,9,14]

Treatment with PEI and RFA is an option for patients with small tumor sizes but who do not meet the criteria for resection or transplantation. Management with RFA demonstrated complete ablation of lesions less than 2 cm in size can occur in more than 90% of cases, with a local recurrence rate of less than 1%. The survival rate after this therapy reached 100% in the first year and 98% in the second year.[5,14]

Transarterial embolization/transarterial chemoembolization (TACE)

Transarterial chemoembolization (TACE) is a technique of administering chemotherapy drugs into the hepatic artery and embolization using a percutaneous technique with fluoroscopy through the femoral artery. The goal of TACE is to exert a strong cytotoxic and ischemic effect on tumor tissue. The drugs used include doxorubicin, mitomycin, epirubicin, 5 fluorouracil, and cisplatin. These drugs are emulsified with lipiodol as a carrier agent, which will selectively remain in the tumor nodule for several weeks to more than 1 year.[5,19]

Most HCC patients are diagnosed at an intermediate-advanced stage (intermediate-advanced stage) based on meta-analysis, only TAE/TACE (transarterial embolization/ chemoembolization) alone has shown reduced tumor growth and may increase the life expectancy of patients with non-resectable liver cancer. TACE with a frequency of 3 to 4 times a year is recommended in patients with good liver function (Child-Pugh A) as well as asymptomatic multinodular tumors without vascular invasion or extrahepatic spread, who are not amenable to radical therapy. Patients with compensated liver function (Child-Pugh B) with a single nodule < 5 cm or multifocal nodules without vascular or extrahepatic tumor invasion are also candidates for TACE. TACE also plays an important role in palliative therapy, but in patients

with liver failure (Child-Pugh B-C), ischemic attacks due to this therapy can cause serious side effects.[5,6,14]

TACE has been widely used in hepatoma therapy non-resectable. This technique has been popularized since 2002, but some experts say that the efficacy of TACE regarding survival in patients with very advanced HCC is still being debated because 4 out of 5 RCTs comparing TAE without treatment, hormone therapy, or chemotherapy failed to show an increase in survival in patients with very advanced HCC. carry on. In general, the indication for TACE is HCC with adequate liver function, no extra-hepatic metastases, and no tumor thrombus in the portal vein, which is also a contraindication for surgery or ablation therapy.[6,14]

In 2021, the Indonesian Liver Research Association developed a consensus regarding the management of HCC, including determining the criteria for patients who are eligible for TACE, absolute and relative contraindications, as well as evaluating the success of the TACE procedure that has been carried out.[6]

Transarterial radioembolization (TARE)

Transarterial radioembolization (TARE) or transarterial radioembolization, or selective internal radiation therapy (SIRT), is another form of local-regional therapy for various clinical variations of KSH. Therapy is carried out by injection of the radioisotope yttrium-90 into the tumor, which results in damage and destruction of the tumor. Yttrium-90 transmits β-rays with a short half-life (2.67 days) and limited penetration capacity (average 2.2 mm-11 mm). Therapy with TARE has a promising effect on tumor response and survival but can cause severe side effects due to the effects of radiation on other organs and sinusoidal obstruction syndrome.[5,14]

To date, there have been no phase III studies demonstrating superior survival usage. TARE has been compared with other alternative treatments, but quite a lot of research has shown similar effectiveness between TARE, TACE, and systemic therapy. TARE can be used in the early stages of liver cell carcinoma as an alternative therapy and bridging to prevent tumor progression in patients awaiting liver transplantation.[5]

Treatment modalities for advanced HCC are initially cytotoxic agents (conventional chemotherapy), hormonal therapy, recombinant interferon alfa-2b, or a combination of two or three of these drugs. Chemotherapy that has been used either alone or in combination includes doxorubicin, cisplatin, and 5-fluorouracil. Various clinical trials conducted after 1980 using only one type of conventional chemotherapy provided a response rate of 0–20%. Combination chemotherapy provides a better response, but several randomized controlled studies have failed to show any benefit in improving survival.[5,6]

Systemic therapy for HCC currently available is generally divided into three, namely molecular targeted therapy, inhibitor immune checkpoint (immunotherapy), and combination immunotherapy with anti-VEGF (atezolizumab and bevacizumab). These three types of systemic therapy do not include systemic chemotherapy because, basically, systemic chemotherapy can kill normal cells while eliminating cancer cells, whereas targeted therapy does not kill normal cells. Targeted chemotherapy is the process that cancer cells need to grow and divide, such as the DNA replication process of cancer cells, while targeted therapy is aimed at abnormal proteins produced by mutated genes (oncogenes) that cause abnormal cell growth.[6,14]

Systemic therapy is indicated for patients with advanced HCC (BCLC C) who have good liver function (Child-Pugh A) and ECOG performance status 0–2 or intermediate stage (BCLC B) but are not suitable (unsuitable) for TACE (transarterial chemoembolization) or have contraindications to TACE or stage B BCLC that has failed or is refractory to TACE.6,35 Not suitable for TACE (unsuitable) is defined as a clinical condition in which TACE may not provide survival benefit or a condition in which TACE may cause harm to the patient. Until now, data regarding the administration of systemic therapy to HCC patients with Child-Pugh B liver function is very

limited.[5,6]

First-line systemic therapy

Sorafenib

Sorafenib is a targeted oral multikinase inhibitor vascular endothelial growth factor (VEGFR 1, 2, and 3); platelet-derived growth factor receptor-β (PDGFR-β); and Raf family kinases (especially C-Raf). Sorafenib was shown to prolong long-term survival rates with a median overall survival (OS) of 10.7 months versus 7.9 months in controls and a time to progression of 5.5 months versus 2.8 months in the control group in a large randomized controlled phase III trial. Sorafenib HCC Assessment Randomized Protocol (SHARP). However, in this study, Sorafenib was given to 95% of HCC patients with Child-Pugh A and only 5% with Child-Pugh B. Since 2007, Sorafenib has been approved by the FDA as a first-line treatment for liver cell carcinoma.[6,14]

Sorafenib is given at a dose of 400 mg 2 times a day, and if side effects occur, interrupt therapy and reduce the dose to 400 mg per day and 400 mg every 2 days. The side effects caused include hand-foot skin reaction, diarrhea, and weight loss.[6,14]

Administration of sorafenib as adjuvant therapy after resection or ablation did not show any benefit, nor did administration of sorafenib simultaneously with TACE. Administration of sorafenib combined with SIRT yttrium-90 also showed no benefit in patient survival.[6,14]

Lenvatinib

Lenvatinib is a multikinase inhibitor of VEGFR1-3, fibroblast growth factor receptor (FGFR1-3), PDGFRα, RET, and KIT. The phase two study of levantinib resulted in a median survival of 18.7 months and was proven to be no less effective than Sorafenib, as proven in the large randomized controlled phase III trial (REFLECT) used in patients with HCC with Child-Pugh A and cases of HCC without operable in 2018. Median overall survival was 13.6 months with lenvatinib and 12.3 months with sorafenib. In this study, the patients involved were patients with relatively good liver function, namely patients with Child-Pugh A criteria.[6,14]

The standard dose of lenvatinib therapy is determined based on body weight (BW), where weight < 60 kg is given a dose of 8 mg per day and weight ≥ 60 kg is given a dose of 12 mg per day, and the overall incidence of side effects is the same between administration of sorafenib and lenvatinib.[6,14]

Atezolizumab and bevacizumab

Atezolizumab is an immunotherapy that selectively inhibits PD-L1 to prevent the interaction of PD-L1 with PD-1 and B7-1 receptors, so it can restore suppressed T cells, while bevacizumab is a monoclonal antibody that inhibits VEGF, so it can inhibit angiogenesis and tumor growth. In the IMbrave150 study, patients in the experimental group received bevacizumab at a dose of 15 mg/kg and atezolizumab at a dose of 1200 mg via intravenous infusion on day 1 of each 21-day cycle. Patients in the control group received sorafenib in a standard dose of 400 mg orally twice daily on days 1–21 of each 21-day cycle. The result was that the atezolizumab-bevacizumab combination provided better 12-month survival compared with the sorafenib group, namely 67.2% versus 54.5%.[6,14]

Atezolizumab-bevacizumab therapy is not recommended in patients with untreated or partially treated esophageal and/or gastric varices, with active bleeding or a high risk of bleeding. Atezolizumab-bevacizumab therapy is also not recommended in patients with a history of bleeding due to esophageal varices and/or gastric varices that occurred within the six months before starting therapy.[6,14]

Second-line systemic therapy

Regorafenib

Regorafenib is the first multikinase inhibitor approved for use as a second-line treatment of HCC intolerance to sorafenib. In a randomized controlled phase III trial conducted on HCC patients in 21 countries, overall survival results were found in advanced-stage HCC patients who received oral regorafenib therapy.[6,14]

Regorafenib is an oral multikinase inhibitor that has more potent inhibitory activity against various angiogenic pathways such as vascular endothelial growth factor receptor (VEGFR 1-3), platelet-derived growth factor receptor (PDGFR)-β, TIE2, and fibroblast growth factor receptor (FGFR) 1), as well as oncogenic pathways (RET, KIT, c-RAF/RAF-1, and BRAF) compared to sorafenib.[6] The efficacy and safety of regorafenib at a dose of 1 x 160 mg per day for three weeks with cycles every four weeks was investigated in a phase III double-blind, randomized study (RESORCE study). Regorafenib provided significant overall improvement benefits when compared with placebo (10.7 vs 7.8 months, HR 0.63, 95% CI 0.5–0.79). In exploratory analysis after this in patients enrolled in the RESORCE study, median survival from initiation of sorafenib was 26 months in the regorafenib group vs. 19.2 months in the placebo group.[6,14]

Ramucirumab

Ramucirumab is a monoclonal IgG anti-VEGF antibody that inhibits angiogenesis by binding to VEGFR2. The efficacy and tolerability of ramucirumab were first tested in the REACH study as second-line therapy after failure with sorafenib or intolerance to sorafenib. This study failed to achieve the primary endpoint with a median survival of 9.2 months in the ramucirumab group versus 7.6 months in the placebo group. Analysis after this showed an improvement in survival in the group of patients with serum AFP levels ≥ 400 ng/dL.[6,14]

Ramucirumab was reinvestigated in the REACH-2 study, which was a phase III study in HCC patients with Child-Pugh A and AFP ≥400 ng/dL. Ramucirumab was proven to improve OS with a median survival of 8.5 months in the ramucirumab group vs 7.3 months in the placebo group and with good tolerance where the side effects that were frequently found were hypertension and hyponatremia.[6,14]

Cabozantinib

Cabozantinib is a tyrosine kinase inhibitor that inhibits c-MET, VEGFR2, and AXL receptors. In a second-line phase III study (CELESTIAL study), including patients who experienced progression on sorafenib therapy and patients who were intolerant to sorafenib. Median overall survival (OS) in the cabozantinib group was 10.2 months, and in the placebo group, it was 8 months (HR 0.76, 95% CI 0.63–0.92). In a subgroup analysis of patients who had received only previous sorafenib (cabozantinib as second-line therapy), cabozantinib therapy remained associated with significantly improved survival (11.3 vs 7.2 months; HR 0.70, 95% CI 0.55– 0.88).[6,13,14]

Side effects that are often found are hand-foot skin reactions, hypertension, diarrhea fatigue and asthenia. The median daily dose of cabozantinib was 35.8 mg; where during the study, it was found that there was a dose reduction in 62% of the sample and 16% of cases discontinued treatment due to side effects.[6,14]

Nivolumab

Nivolumab is a human monoclonal antibody IgG4 that interferes with the immune checkpoint signal programmed protein death-1 (PD1), thus restoring the anti-tumor effector activity of T cells attacking cancer cells. Globally, single-arm phase I/II study CheckMate 040 of nivolumab in 262 patients with advanced HCC who did not respond to sorafenib or had never received sorafenib, or were intolerant to sorafenib, showed an objective response rate of 20% with a 9-month survival rate reaching 74% in patients treated with a dose of 3 mg/kgBW, and with an acceptable safety profile. Based on promising results from this global trial, the FDA in 2017 granted accelerated approval for the use of nivolumab as a second-line treatment for liver cell carcinoma.[6,14]

In another study compared the efficacy of nivolumab versus sorafenib as first-line treatment for advanced HCC. This phase III trial (CheckMate 459) randomized 726 patients to nivolumab or sorafenib in a 1:1 ratio. Median survival was 16.4 months for

patients receiving nivolumab and 14.7 months for those receiving sorafenib, which was not statistically significant.[6,14]

Pembrolizumab

Pembrolizumab is another anti-PD-1 monoclonal antibody used to treat liver cell carcinoma. On a non-randomized, multicenter, open-label, single, a phase II trial (KEYNOTE 224), administered pembrolizumab to patients with advanced HCC who had previously been treated with sorafenib and demonstrated an objective response rate of ±17%, patients were able to achieve a durable response, with 56% maintaining the response up to more than 1 year. The dose of pembrolizumab given is 200 mg intravenously every three weeks, given on the first day of each three-week cycle, for up to 35 cycles (approximately two years), or until the disease progresses or the patient experiences intolerable side effects. Based on these promising initial results, the FDA granted approval for pembrolizumab as a second-line treatment for hepatocellular carcinoma.[6,14]

Pembrolizumab failed to demonstrate a substantial benefit for patient survival in a randomized controlled phase III trial of 413 patients with advanced HCC who experienced radiographic progression or intolerance to sorafenib. These negative results from the study design of phase III trials highlight that the key to successful phase III trials is caution with immunotherapy, and combination treatments may be necessary.[6,14]

2. Conclusion

Hepatocellular carcinoma (HCC) is a malignant tumor originating from hepatocytes with a high incidence and a very poor prognosis. The symptoms caused by HCC in the early stages are often unclear and disguised by other liver disorders, so most cases of HCC are found at an advanced stage. HCC management in Indonesia is carried out according to the HCC management algorithm established by PPHI, which refers to the APASL algorithm. Current management of HCC focuses on systemic therapy with a focus on a combination strategy of immunotherapy or a combination of targeted therapy with immunotherapy as the first line.

3. References

1. Budihusodo U. Hepatocellular carcinoma in the textbook of internal medicine volume 3. 6th ed. Jakarta: Balai Penerbit Fakultas Kedokteran Universitas Indonesia. 2014; 3040–6.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A. Global cancer statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA CANCER J CLIN 2021; 71: 209–49.
3. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB, et al. Utilization of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology. 2010; 52(1): 132–41.
4. Jasirwan COM, Hasan I, Sulaiman AS, Lesmana CR, Kurniawan J, Kalista KF et al. Risk factors of mortality in the patients with hepatocellular carcinoma: a multicenter study in Indonesia. Current Problems in Cancer. 2019; 14(15): 1–11.
5. Lesmana LA, Waspodo AS, Gani RA, Hasan I, Siregar L, Sulaiman AS, et al. National consensus on the management of hepatocellular carcinoma. Perhimpunan Peneliti Hati Indonesia. 2017.
6. Hasan I, Setiawan PB, Djumhana A, Purnomo HD, Siregar L, Gani RA, et al. National consensus on systemic therapy of hepatocellular carcinoma in Indonesia. Perhimpunan Peneliti Hati Indonesia. 2021.
7. Rasyid A. The importance of radiology in early detection and treatment of primary liver cancer. USU Press. 2006.
8. Heimbach J, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD Guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2017; 67(1): 358–80.

9. Janevska D, Chaloska-Ivanova V, Janevski V. Hepatocellular carcinoma: risk factors, diagnosis and treatment. Macedonian Journal of Medical Sciences. 2015; 3(4): 732–6.
10. Alwi I, Salim S, Hidayat R, Kurniawan J, Tahapery DL. Hepatoma in clinical practice guides management in internal medicine. Jakarta: Interna Publishing. 2019; 244–9.
11. Nurdjanah S. Liver cirrhosis in Textbook of Internal Medicine Volume I. 6th ed. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia. 2014.
12. Chao WL, Tsai HI, Lee WC, Huang SW, Lin CY, Hsieh YC, et al. Normal alpha-fetoprotein hepatocellular carcinoma: Are they really normal? Journal of Clinical Medicine. 2019; 8(10): 1736.
13. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo B, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. The New England Journal of Medicine. 2018; 379(1): 54-63.
14. Yang JD, Heimbach JK. New advances in the diagnosis and management of hepatocellular carcinoma. BMJ. 2020; 371: m3544.