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TINJAUAN PUSTAKA—*LITERATURE REVIEW*

Treatment Options for Patient with Unresectable Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is a primary liver cancer that occurs due to the abnormal growth of hepatocytes. HCC is one of the cancers with the highest prevalence and incidence in the world. The main risk factors for HCC in Indonesia are chronic infection with hepatitis B virus, hepatitis C virus, and liver cirrhosis. The selection of the appropriate treatment modality for each patient is based on several patient-specific characteristics, such as tumor size, location, portal vein thrombosis, and liver function. Treatment options for unresectable hepatocellular carcinoma include intra-arterial therapy, multikinase inhibitors, and immunotherapy. Determining the stage is an important part of managing HCC because it can determine the treatment. One of the staging systems is the Barcelona Clinic Liver Cancer (BCLC) which categorizes HCC into 5 stages. Clinical severity criteria with BCLC stage are often used because they have good validity in predicting the prognosis of HCC patients.

Keywords: Hepatocellular Carcinoma, Treatment

INTRODUCTION

Hepatocellular carcinoma (HCC) is a kind of primary liver cancer caused by abnormal hepatocyte cell growth. HCC is one of the most common cancers in the world, having a high frequency and incidence. HCC has an incidence of 841,080 cases in 2018 and is expected to reach 905,677 cases in 2020, making it the world's fifth most frequent cancer and the fourth leading cause of death (with 781,631 cases).[1] Southeast Asia is ranked second in the incidence of liver tumors globally, and Indonesia is ranked third after Vietnam and Thailand. This incident proves that HCC incidents in Indonesia have a fairly large portion. HCC is 10-20% of all liver diseases in Indonesia. HCC is most commonly found in people over the age of 50-70 years and is more common in men than in women, with an incident ratio of 2-4: 1. The main risk factors for HCC in Indonesia are chronic hepatitis B virus, hepatitis C virus, and cirrhosis of the liver with various causes.[2]

Many HCCs cannot be surgical resectioned because of the tumor's size, location, or poor liver function. The selection of appropriate treatment modalities for each patient is based on specific patient characteristics, such as tumor size, location, portal vein thrombosis, and liver function. A common barrier to HCC therapy is that the disease almost always develops in a chronically inflamed liver. Many efforts have improved patient survival by conducting Clinical trials investigating local and systemic treatment options for patients with these unresectable tumors. Therapeutic options for HCC include intra-arterial therapy, multikinase inhibitors, and immunotherapy. [3]

Determination of the stage becomes an essential part of managing HCC because it can determine the therapy to be taken. One of the stadium systems used is the Barcelona Clinic Liver Cancer Group (BCLC), categorizing HCC into five stages (0, A, B, C, and D). Clinical severity criteria with Barcelona Clinic Liver Cancer (BCLC) are most commonly used because they

have sufficient validity in predicting the prognosis of HCC patients.[1]

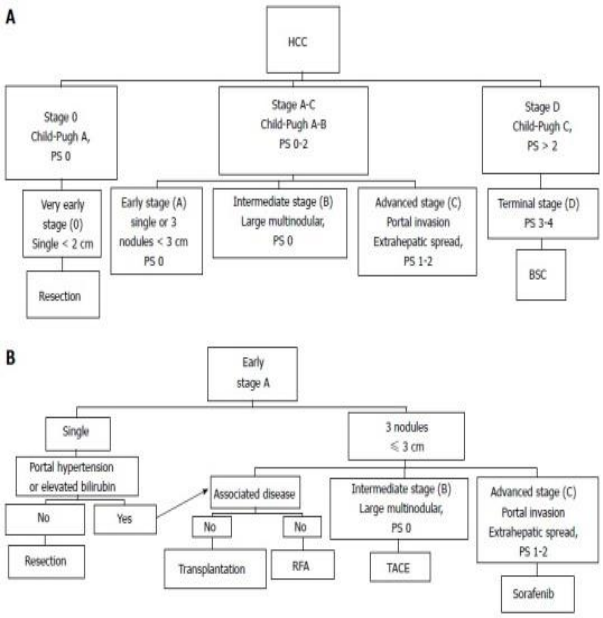

Figure 1. Barcelona Clinic Liver Cancer Algorithm[4]

BCLC 0 phase is defined as the very early stage. Patients exhibiting well-maintained liver function (Child-Pugh A) are diagnosed with one asymptomatic nodule measuring less than 2 cm without vascular invasion. BCLC A phase is defined as an early-stage disease, a patient with Child-Pugh status A or B who is diagnosed with one nodule or a maximum of three nodules measuring <3 cm. BCLC B phase is defined as a mid-stage disease, i.e., a patient with Child-Pugh grade A or B status, diagnosed with multiple nodules without vascular invasion or extrahepatic metastasis. BCLC C phase is defined as advanced disease, i.e., patients with Child-Pugh A or B, vascular invasion or extrahepatic metastasis, and cancer-related symptoms (PS 1-2). BCLC D phase is defined as a terminally staged disease, i.e., a patient with a degree of Child-Pugh C at each tumor stage and cancer-related symptoms (PS>2).

The BCLC system provides treatment recommendations for each phase based on the best treatment options currently available. For patients with stage 0 and A status, curative treatment options are recommended, such as surgical resection, liver transplantation, and ablation. Meanwhile, TACE is recommended for patients with stage B status. Sorafenib, a multikinase inhibitor, is recommended for patients with stage C status, and supportive care is recommended for stage D status.[4]

THERAPY

1. Intra-arterial Therapy

Transarterial Embolization (TAE) / Bland Embolization

The basic principle of this therapy is to inhibit the flow of hepatic arteries that give blood to tumor cells to cause ischemia in those cells. Patient selection for all locoregional treatments, including TAE, involves clinical and serological evaluations. It includes functional status trials, liver function trials, and clinical indices such as ALBI (Albumin-Bilirubin), CP (Child-Pugh), MELD (Model for End-stage Liver Disease), and ECOG (Eastern Cooperative Oncology Group) performance status scores for stratification and patient assessment.[5]

According to Gbolahan (2017), overall, embolism therapy outperforms supportive therapy in terms of survival. Based on a meta-analysis of Tsochatzis, *et al.* 2014 comparison between TAE and TACE found no significant difference in overall survival. Lee and Khan, 2017 also concluded there were no significant differences in side effects, RECIST response, and survival rate. Kluger, *et al.* 2014 discovered that patients who received TAE had a lower chance of receiving re-therapy before transplantation.

Transarterial Chemoembolization (TACE)

TACE involves the same occlusion of tumor vessels as TAE. However, TACE allows the administration of chemotherapy given at once with embolism therapy. In the conventional approach (c-TACE), lipiodol zed chemotherapy agents are administrated into the arteries, followed by embolism agent.[9] Newer approaches using drug-eluting beads (DEB-TACE) provide better standardization and lower hepatotoxicity. In DEB-TACE, chemotherapy is released through microsphere.[10]

The most appropriately indicated candidates for TACE are patients with intermediate-stage HCC (BCLC grade B, Child-Pugh B or better) without portal vein thrombosis or extrahepatic spread who are not eligible for surgical resection or transplantation. Several

studies confirm that TACE can significantly affect survival if patients are selected based on the factors mentioned above.

The difference in therapeutic outcomes between c-TACE and DEB-TACE is still controversial because no analysis confirms the OS difference between the two.[11] The combination of locoregional therapy with systemic chemotherapy has been studied in space trials that compare DEB-TACE patients. It combined with sorafenib with DEB-TACE combined with placebo. Still, the results of the tests show no significant improvement.[12]

Transarterial Radioembolization (TARE)

According to Kennedy, *et al.* 2017 this procedure is based on the main principle of providing therapeutic effects through radiation. Currently, radioisotope yttrium, 90Y, is implanted into a microsphere injected into a branch of the hepatic artery that gives tumor cells blood flow. 90Y occurs during beta decay and shines a light on the surrounding tumor, which ultimately impairs the repair mechanism and facilitates cell death.

According to Lobo's meta-analysis (2016), the results of OS and the degree of TARE complications are the same as for TACE. Premiere trials results showed a longer time to progression (TTP) in patients with TARE therapy. In a prospective study by Salem (2018), excellent results with OS were reported at 47.3 months for Child-Pugh A patients and 27 months for Child-Pugh B patients. BCLC 0 or BCLC A patients may be given TARE therapy with radiation segmentectomy.

Ablation

Ablation techniques for HCC include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA). Also, irreversible electroporation (IRE), laser-induced interstitial thermotherapy (LITT), and high-intensity focused ultrasound (HIFU).[5]

Curative ablation is an effective alternative to resection, especially for tumors smaller than 3 cm. According to Heimbach, *et al.* 2018 RFA and MWA may also be considered in advanced patients (BCLC C) to be lowered as a bridge to transplantation and intermediate-stage patients (BCLC B) when combined with TACE.

OS results between RFA and resection did not differ significantly at 1 and 3 years.[15] Comparison of ablation with RFA and MWA shows a slower degree of tumor development in MWA than RFA.[16] Comparison between CA and RFA shows CA has a higher degree of survival for three years and slower tumor development than RFA.[17] The combination of MWA with TACE is effective for lesions of 3-5 cm.

2. Multikinase Inhibitor

Sorafenib

Sorafenib (SOR) is the first oral multikinase inhibitor (MKI) approved and recommended for unresectable HCC patients as a first-line. Sorafenib inhibits tumor angiogenesis and tumor proliferation by blocking tyrosine kinase receptors (VEGFR-2/3, PDGFR-β, c-KIT, FLT-3, RET), downstream line kinase activity (Ras/Raf/MEK/ERK, JAK/STAT), and other targets (c-Raf, B-Raf).[18] Two necessary studies have tested and demonstrated the success of sorafenib for patients. It means for patients with unresectable HCC in SHARP trials in Europe, North America, South America, Australia, and Asia-Pacific. The study trials have significantly increased the median OS (Overall Survival) by about 2.8 months with oral sorafenib 400 mg twice a day.[18,19]

Sorafenib has been approved as the first line of treatment for unresectable HCC patients, but it is difficult to tolerate. Complex tolerance for patients with sorafenib treatment makes them reduce the dose and even stop therapy due to the side effects of sorafenib. There are some of the most common side effects, such as hypertension (42%), diarrhea (39%), decreased appetite (34%), reduced weight (31%), and fatigue (30%).[19] In the Qin et al. (2019) study, sorafenib and Lenvatinib had a median life expectancy of about one year. Zhang, *et al.* (2020) said the survival of patients with unresectable HCC multikinase inhibitor sorafenib only lasted for an estimated three months.[19,20]

Lenvatinib

Lenvatinib is also a treatment option for patients with unresectable HCC in an advanced stage.[20] Compared to sorafenib, another multikinase inhibitor, Lenvatinib, was approved in

2018 because it has good survival benefits for unresectable HCC patients.[20] Lenvatinib targets several receptors as Tyrosine Kinase Inhibitors (TKI), namely VEGFR 1-3, PDGFR-α, Fibroblast Growth Factor Receptor 1-4 (FGFR 1-4), KIT, and Rearrangement During Transfection (RET).[21]

Lenvatinib is used as a first-line treatment and as a second-line treatment for HCC unresectable patients who are intolerant to sorafenib and third-line therapy if sorafenib and regorafenib fail due to the success, tolerability, and cost-effectiveness of Lenvatinib.[22]

Patients with Lenvatinib treatment had an average overall survival of 13.6 months. There are the most common side effects of Lenvatinib, such as hypertension (42%), decreased weight (31%), and proteinuria (25%).[19]

Regorafenib

Regorafenib is the second line of treatment for unresectable HCC patients who failed sorafenib.[19,20] In structure and function, regorafenib is similar to sorafenib. However, regorafenib tends to suppress VEGFR signals and has anti-angiogenic effects that are different from.[18] Regorafenib is a diphenylene multikinase oral inhibitor that targets angiogenic (VEGFR1-3, TIE2), stroma (PDGFR-b, FGFR), and oncogenic receptor tyrosine kinase (KIT, RET, and RAF).

Compared to placebo, regorafenib had a more significant PFS and overall survival (OS).[23]

Regorafenib inhibits several activities at clinically achievable treatment concentrations, such as RET, VEGFR 1-3, KIT, PDGFR-α, PDGFR-β, FGFR1 FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl. Regorafenib has a standard dose of 160 mg once daily in tablets and after the last dose can last for 48 hours by being correlated with inhibition of tumor growth (TGI).[23]

The FDA has approved regorafenib as a treatment for patients with advanced HCC unrespectable that developed sorafenib in 2017. [23] The RESOURCE phase III trials in the Tomonari, *et al.* (2020) study states that regorafenib experienced a median OS increase for 2.8 months with a reduced risk of death by 38%. Also, it had tolerance in patients with unresectable HCCs as an antitumor activity.[22,23]

3. Immunotherapy

3.1 Introduction

Immunotherapy in unresectable HCC is the same as cancer immunotherapy in general, involving immune system molecules, especially cytotoxic T cells and natural killer cells (NK). Neoantigens primarily from dead tumor cells or gastrointestinal microbiota presented by antigen-presenting cells (APCs) primarily by dendritic cells to T cells in lymphonodi cause hepatocellular carcinoma-specific T cells activation. These cytotoxic T cells will infiltrate the tumor area to recognize and kill tumor cells. The development of adoptive T cell transfer therapy aims to improve the cytotoxic ability of tumor cells through the extraction of patient immune cells, stimulation, and expansion in vitro, and transfer back to the patient's body.[24]

Intrahepatic conditions that are physiologically tolerogenic to prevent the body's overreaction to actual harmless molecules through high Treg differentiation led to increased expression of immunosuppressant cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), increased expression of coinhibitory molecules such as programmed cell death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), and decreased costimulatory immune receptors. These immunosuppressive conditions cause ideal conditions for the growth and development of malignant cells, so immune checkpoint inhibitor (ICI) drugs are developed.[25]

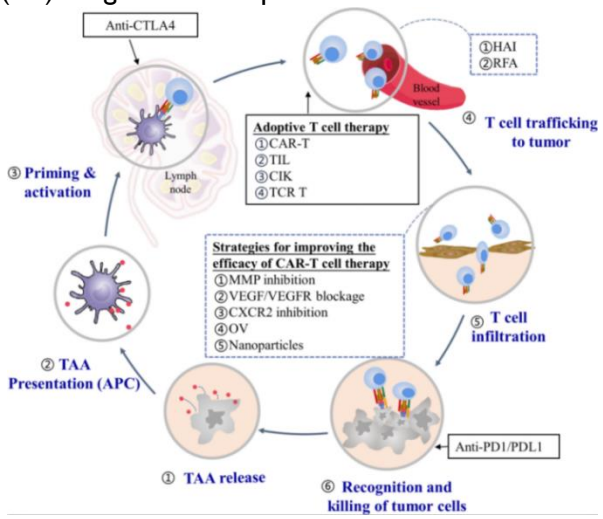

Figure 2. HCC Pathogenesis and Immunotherapy Mechanism of Action[20]

3.2 Adoptive T cell therapy

3.2.1 Cytokine-induced killer (CIK) cell

This cell population is derived from lymphocytes cultured with recombinant human interferon-γ (IFN-γ), anti-CD3 antibody, or recombinant human interleukin-2 (IL-2). CIK consists of NK cells (CD3−CD56+), NKT cells (CD3+CD56+) and cytotoxic T cells (CD3+CD56−). Phase III domesticated research reveals that CIK injection increases the duration of free recursion for 14 months.[26]

3.2.2 Tumor-infiltrating lymphocytes (TILs)

These cells are derived from the isolation of tumor specimens with dominant cell subtypes in the form of T cells. Clinical studies show patients with high CD8+ TILs have good overall survival (OS).[27]

3.2.3 TCR cell therapy

TCRs consist of 2 protein chains, i.e., α and β, with multiple populations expressing γ and δ. Through the inertia of the TCR gene to human T cells with γ-retrovirus or lentivirus can form stable, high-definition T cells. Clinical trials of this therapy are still being conducted.

3.2.4 CAR-T cell therapy

Chimeric antigen receptor (CAR) T cell therapy targets CD19 in hematological malignancies. This therapy for HCC does not show efficiency and specificity as expected, so it is still in development stage [28]. Molecular targets that are still being developed include:

- Glypican-3 (GPC-3): there are 14 ongoing Clinical trials;
- Mucin-1 (MUC-1): There are two-phase i/II Clinical trials underway;
- α-Fetoprotein (AFP): There is a PHASE I trial that tests for T1402L1-CAR T cells (anti-HLA-A02/AFP complex) which shows 3 out of 6 patients experience a decrease in tumor size without cytokine-responding syndrome and neurotoxicity;
- Carcinoembryonic antigen (CEA): This therapy is tolerated in Clinical trials of second-generation G CAR-T cells, i.e., six patients with liver metastasis show good tolerance results, especially in patients with extensive liver metastasis;[29]
- Epithelial cell adhesion molecule (EpCAM): There are phase I and phase I/II Clinical trials in the process of being trialed.

3.3 Immune checkpoint inhibitor (ICI)

3.3.1 Nivolumab

Nivolumab is an IgG4 antibody against PD-1. This drug is a second-line therapy in patients who were previously treated with sorafenib. In phase II Clinical trials, CheckMate, 40 out of 22 respondents (91%) survived for at least six months, and 55% survived for at least 12 months.[30]

3.3.2 Pembrolizumab

Pembrolizumab is an IgG antagonist that inhibits the interaction of PD-1/PD-L1 or PD-L2. Based on clinical trials, phase II, Keynote-224 found that this therapy can be tolerated with a median overall survival (OS) of 12.9 months in patients given intravenous pembrolizumab every three weeks for two years.[31]

CONCLUSIONS AND RECOMMENDATIONS

A summary of the advantages of intra-arterial therapy can be seen in table 1.

Table 1. Summary of Advantages between Intraartrial therapy

Modalities	Advantages
TAE	OS is better than the best supportive care Avoiding chemotherapy toxicity Cheaper than TACE
TACE	OS is better than the best supportive care Can provide embolic and chemotherapy effects continuously
TARE	Have a slower tumor progressiveness (TTP) time than TACE so that the quality of life is better than TACE
Ablation	Has the same good results as tumor resection < 3 cm

After considering the advantages of intra-arterial therapy and adjusting to the BCLC algorithm, it can be seen that TAE, TACE, TARE, and ablation can be used for treatment in patients

with BCLC B. The recommended combination therapy for BCLC B patients is ablation therapy with TACE. Patients with BCLC A or BCLC 0 who are not resection candidates may be given ablation or ablation therapy with TACE or transplantation. If the patient is unable to perform ablation, TARE can be performed with radiation segmentectomy.

A summary of systemic chemotherapy can be seen in table 2.

Table 2. OS Summary between Chemotherapy

Modalities	OS
Sorafenib	OS 2.8 months to 12 months
Lenvatinib	OS 13.6 months
Regorafenib	OS 12 months

Based on the criteria of REFLECT, the selection between sorafenib and Lenvatinib as first-line therapy is as follows:

- Sorafenib is better if the tumor occupies the liver > 50%, there is an invasion of biliary ducts or port veins, chronic hepatitis C infection, AFP < 200 ng/mL, Child-Pugh B, above 75 years of age, infected with HIV, receiving a renal transplant, or suffering from chronic kidney disease.
- Lenvatinib is better if the tumor occupies the liver <50%. There is no invasion of biliary ducts or port veins, chronic hepatitis B infection, AFP > 200 ng/mL, child Pugh A, under 45 years of age.
- Second-line therapy is adapted to the first-line therapy given. If sorafenib is first-line therapy for regorafenib, it can be given as second-line therapy. If Lenvatinib is reached the first line, sorafenib is given as second-line therapy.

The summary of immunotherapy, especially ICI, can be seen in table 3.

Table 3. OS Summary between ICI

Modalities	OS
Nivolumab	OS 6-12 months
Pembrolizumab	OS 12.9 months

The use of immunotherapy is still relatively new and has been growing rapidly in recent years. Clinical trials that have been done are limited. Based on completed trials, nivolumab and pembrolizumab are indicated as second-line therapies. Still, if combined, such as nivolumab combined with cabozantinib or ipilimumab, they can be given first-line therapy. The combination of pembrolizumab and Lenvatinib has also been accepted for use as first-line therapy.

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