Treatment for Intermediate-stage Hepatocellular Carcinoma: Current Practice and Outcome in Real World Study

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ABSTRACT

Background: *Intermediate-stage hepatocellular carcinoma (HCC) is a very heterogeneous disease. The first line treatment for this group is transarterial chemoembolization (TACE), however, in clinical practice, not all patients are suitable for TACE. We aim to evaluate current treatment practice and outcome of patients with intermediate-stage HCC.*

Method: *HCC patients database from 2013 to 2016 in Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital were retrospectively analyzed. Patients with intermediate-stage HCC were included in this study.*

Results: *A total of 456 patients were diagnosed with HCC, but only 151 (33.1%) patients with intermediate-stage HCC were included. Men outnumbered women in a ratio of 3:1. The most common etiology for HCC was hepatitis B virus (HBV) infection, which accounted for 55% of patients. Fifty-four patients (35.7%) were treated with TACE as first-line treatment. Sixty-seven patients (44%) were given best supportive care due to ineligibility for TACE. Frequency of TACE varied from one to eleven times. Overall median survival was 617 days (1.7 years). One-year survival for patients undergoing TACE and liver resection was 47% and 60%, respectively. We did not compare the survival between any treatment groups because the number of patient in each group is not sufficient to be statistically analyzed.*

Conclusion: *Only 35.7% of patients with intermediate-stage HCC was treated with TACE as first-line treatment. An improvement in the treatment strategy should be done for HCC patients in Indonesia.*

Keywords: *hepatocellular carcinoma, intermediate-stage, treatment, outcome*

ABSTRAK

Latar belakang: *Karsinoma sel hati (KSH) stadium menengah adalah suatu keadaan yang sangat heterogen. Terapi lini pertama untuk kelompok ini adalah transarterial chemoembolization (TACE). Akan tetapi, dalam praktik sehari-hari, tidak semua pasien layak untuk dilakukan TACE. Tujuan penelitian ini adalah menilai tatalaksana yang dilakukan untuk pasien KSH stadium menengah dan luaran yang dihasilkan.*

Metode: *Data registrasi pasien KSH tahun 2013 – 2016 di RS Cipto Mangunkusumo dan RS Kanker Dharmais dianalisis secara retrospektif. Pasien dengan KSH stadium menengah dimasukkan dalam studi ini.*

Hasil: *Sepanjang periode 2013 – 2016, terdapat 456 pasien yang didiagnosis dengan KSH, namun hanya 151 (33,1%) yang didiagnosis sebagai stadium menengah dan diikutsertakan dalam penelitian ini. Jumlah pasien laki-laki lebih banyak dibandingkan perempuan dengan perbandingan 3:1. Penyebab tersering KSH adalah infeksi virus hepatitis B (VHB), yang ditemukan pada 55% pasien. Sebanyak 52 pasien (34,4%) dilakukan TACE sebagai terapi lini pertama. Sebanyak 67 pasien (44%) diberikan terapi suportif karena tidak layak untuk TACE. Frekuensi TACE bervariasi antara satu sampai tujuh kali. Median kesintasan keseluruhan adalah 617 hari (1,7 tahun). Kesintasan satu tahun pasien yang menjalani TACE sebesar 47%, sedangkan yang menjalani reseksi hati sebesar 60%. Perbandingan kesintasan antarkelompok terapi tidak dilakukan karena jumlah pasien dalam tiap kelompok tidak mencukupi untuk dilakukan analisis statistik.*

Simpulan: *Hanya 34,4% pasien KSH stadium menengah yang dilakukan TACE sebagai terapi lini pertama. Perbaikan strategi terapi harus dilakukan bagi pasien KSH di Indonesia.*

Kata kunci: *karsinoma sel hati, stadium menengah, terapi, luaran*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide.[1] Most of the patients are usually diagnosed at late stage, when curative treatment is no longer suitable. Moreover, HCC is usually associated with advanced chronic liver disease, which contributes to the patients' prognosis and survival. Several systems have been proposed for HCC staging in purpose for the treatment of choice, and the most well-known staging system is the Barcelona Clinic Liver Cancer (BCLC) staging system, which includes treatment allocation for each stage.[2,3]

Patients classified as intermediate-stage are typically those with good performance status, single to multiple huge tumors, and various stages of liver function without any extrahepatic metastasis or vascular invasion.[2,3] According to the BCLC staging system, the recommended treatment approach for this group of the patients is trans arterial chemoembolization (TACE).[4] However, in the real-life practice, not all patients are suitable candidates for TACE and not all patients have the access or chance for treatment with TACE.

Resources, equipment, and expertise are required for TACE and other treatment modalities, such as radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT), and selective internal radiation therapy (SIRT). Systemic therapy for HCC is not covered by our national health insurance. TACE and other HCC treatment modalities are only available in several tertiary hospitals in big cities. Therefore, in this study, we aim to evaluate current treatment practice and outcome of patients with intermediate-stage HCC who are referred to our hospitals from all over the country.

METHOD

A retrospective analysis was done from HCC patients' database from 2013 to 2016 in Cipto Mangunkusumo Hospital and Dharmais National Cancer Hospital. HCC was diagnosed based on the 2009 Asian Pacific Association for the Study of the Liver (APASL) guidelines or the European Association for the Study of the Liver - European Organization for Research and Treatment of Cancer (EASL-EORTC) clinical practice guidelines.[5,6] HCC was diagnosed based on a multiphasic computed tomography (CT) scan or magnetic resonance imaging where lesions showed arterial hyper-vascularity and venous washout, in a background of chronic liver disease. Lesions that did not display the typical pattern of HCCs were subjected to liver biopsy. After the diagnosis of HCC was confirmed, patients were staged according to the BCLC staging system. Intermediate-stage (BCLC-B) patients were included in this study.

Survival was measured from the date of diagnosis (first presentation of HCC) to the date of death or last follow-up. All parameters investigated were measured before any treatment and within four weeks of diagnosis. Treatment was classified as first-line, second-line, and third line according to the sequence of treatment modalities given by the clinicians. For example, first-line means the first treatment modality given to the patient.

The majority of treatment decisions were made according to EASL-EORTC guidelines for HCC. Curative treatment, such as surgical resection or RFA, was considered when there was a possibility that all tumors could be eradicated by hepatectomy, RFA, or the combined use of both approaches. On the other hand, when the waiting-time for TACE was too long or when there were contraindications for TACE, the patients would be offered other treatment modalities, such as sorafenib or stereotactic body radiation therapy,

when appropriate. Between 2013 and 2016, sorafenib was the only systemic therapy approved for HCC.

All statistical analysis was undertaken using the statistical package for the social sciences (SPSS) 20.0 software. Continuous data were expressed as the mean ± standard deviation (SD) if the distribution was normal and as median value with interquartile range if the distribution was not normal. Categorical variables were expressed as absolute and relative frequencies. The overall survivals were obtained using the Kaplan-Meier method.

RESULTS

Over the period of the study, a total of 456 patients were diagnosed with HCC, but only 151 (33.1%) of patients with intermediate-stage HCC were included in this study. Of these, 88 (58.3%) patients were from Cipto Mangunkusumo Hospital, while the rest were from Dharmais Hospital. Men outnumbered women in a ratio of 3:1. The most common etiology for HCC in our patients was hepatitis B virus (HBV) infection, which accounted for 55% of patients, followed by non-B non-C etiology and hepatitis C infection, respectively. A total of 51 patients (33.8%) had largest tumor diameters of >10 cm.

Table 1. Patient background and tumor characteristics

Variable	n = 151 n (%)
Sex, n(%)	
Men	114 (75.5)
Women	37 (24.5)
Age, median (interquartile range), years	58 (16)
Child-Pugh, n (%)	
Class A	107 (70.9)
Class B	41 (27.2)
No data	3 (1.9)
Alpha feto-protein, n (%), ng/mL	
< 200	65 (43.0)
≥ 200	74 (49.0)
No data	12 (8.0)
Etiology, n (%)	
Hepatitis B	83 (55)
Hepatitis C	25 (16.6)
Non-B Non-C	36 (23.8)
Hep B and Hep C	4 (2.6)
No data	3 (2)
Largest tumor diameter	
≤ 5 cm	7 (4.6)
> 5 – 10 cm	64 (42.4)
>10 cm	51 (33.8)
No data	29 (19.2)
Presenting symptom, n (%)	
Symptomatic	141 (93.4)
Asymptomatic	10 (6.6)

Table 2. Treatment modalities

	n = 151 n (%)
First-line treatment, n (%)	
Transarterial chemoembolization	54 (35.7)
Resection	11 (7.2)
Transarterial chemo-infusion	9 (6.0)
Stereotactic body radiation therapy	3 (2.0)
Sorafenib	3 (2.0)
Radiofrequency ablation	3 (2.0)
Percutaneous ethanol injection	1 (0.7)
Best supportive care	67 (44.4)

Fifty-four patients (35.7%) were treated with TACE as first-line treatment (Table 2). Sixty-seven patients (44%) were given best supportive care due to ineligibility for TACE. The number of TACE sessions varied between 1–11 times. Overall median survival was 617 days (1.7 years). The one-year survival rate of patients treated with TACE was 47%, while that of patients treated with liver resection was 60%. We did not compare the survival between any treatment groups because the number of patients in each group was not sufficient to be statistically analyzed. As many as 24 patients received other treatment modalities after the first-line treatment, including resection, TACE, sorafenib, SBRT, RFA, and transarterial chemoinfusion (TACI). Furthermore, three patients were treated with sorafenib and one patient with RFA due to disease progression after their second-line treatment.

We broke down treatment modalities for patients with Child-Pugh A and B (Table 3). Patients eligible for TACE were mostly Child-Pugh A. However, as many as 35 patients with Child-Pugh-A were provided with best supportive care and did not get the opportunity for any palliative or curative treatment option. Among patients provided with best supportive care, 40.3% had the largest tumor diameters of more than 10 cm and 31.3% had tumor diameters of >5 – 10 cm (Table 4).

Table 3. Comparison of Child-pugh classification among first-line treatment

	TACE	Resection	RFA	PEIT	SBRT	Best supportive care
Child-Pugh A	46	10	1	0	2	35
Child-Pugh B	8	0	1	1	1	29
No data	0	0	0	0	0	3

PEIT: percutaneous ethanol injection therapy; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; TACE: transarterial chemoembolization

Table 4. Largest tumor diameters and chance for any kind of treatment

Tumor diameter	Any treatment n = 84	Best supportive care n = 67
≤ 5 cm	6 (7.1)	1 (1.5)
> 5 – 10 cm	43 (51.2)	21 (31.3)
>10 cm	24 (28.6)	27 (40.3)
No data	11 (13.1)	18 (26.9)

DISCUSSION

Patients classified as intermediate-stage HCC should have preserved liver function with single large solitary tumors (> 5 cm) or large multifocal HCC nodules in both lobes of liver, without any vascular invasion or extra-hepatic spread, and should have no symptoms or have a performance status of 0 according to the Eastern Cooperative Oncology Group (ECOG) scale.[7] Since patients with a large tumor burden affecting both lobes usually have cancer-related symptoms, they are more suitable to be classified as having advanced stage disease, instead of intermediate-stage disease. In this study, as many as 93.4% of patients were symptomatic but classified as intermediate-stage disease based on the tumor burden and liver function. As performance status is a prognostic factor for HCC, this may contribute to the poor one-year survival rate of our patients treated with TACE, which was at 47%. A high one-year mortality rate of 34.1% was also reported by Lin et al and they concluded that Child-Pugh B and high serum AFP were the independent risk factors for mortality.[8]

Until recently, TACE was considered the only first-line treatment for intermediate-stage HCC since it was the only treatment modality consistently showed survival benefit in this group.[9-11] However, there was a changing paradigm that patients who were unsuitable for TACE should be treated initially with systemic therapy.[12] In this study, there were 51 patients (33.8%) with largest tumor diameters of >10 cm, who fulfilled the criteria of unsuitable for TACE. Of these 51 patients, 27 patients were provided with best supportive care, as mentioned in Table 4. This group of patients were those who might get benefit from early administration of systemic therapy. Nonetheless, between 2013 and 2016, systemic therapy for patients with intermediate-stage HCC was not a common practice mainly due to its high cost. Moreover, systemic therapy for HCC has not been covered by our national health insurance until now. Therefore, as many as 44.4% of the total patients included in this study only received best supportive care (Table 2). Long wait times between diagnosis and TACE might as well contribute to the deterioration of liver function or the increase in tumor burden that might hinder the patients from receiving TACE. Patients who gave partial response or got stable disease after their first TACE session were continued with second TACE session until they progressed.[13] With the changing paradigm of earlier administration of systemic therapy, patients unsuitable for TACE might have better prognosis.

The concept of intermediate-stage sub-classification by tumor burden and liver function was proposed by some groups.[14,15] This sub-classification can assist clinicians in selecting patients unsuitable for TACE. However, the application of the sub-classification needs greater efforts, especially in a center with a high volume of patients. Some clinicians are not familiar with the sub-classification. Therefore, the presence of a multidisciplinary team (MDT) can assist in the treatment decision process. Our hospitals have applied the MDT approach since 2013 and patients unsuitable for TACE were mostly provided with best supportive care during this study period.

In our series, there were ten patients who underwent liver resection. Current BCLC staging system only recommends liver resection for patients with very-early (BCLC 0) or early (BCLC A) stage HCC. Liver resection for intermediate-stage HCC was conducted in many medical centers. A recent systematic review of 50 studies involving 14,808 participants reported that one-year and five-year survival rate of patients with large/multinodular HCC undergoing liver resection were 81% and 42%, respectively.[16] This outcome was better than our patients whose one-year survival rate was only 47%. Therefore, selection process is very important in achieving better results. Tada et al.[17] found that liver resection in patients with Child-Pugh score of 5 and ≤ 3 tumors, especially 2 tumors, resulted in a higher survival rate than that of TACE.

Limited access for treatment might also contribute to the low number of patients receiving any kind of definitive therapy. Indonesia is one of the developing countries in Asia Pacific region, with a high number of HCC patients, due to a high prevalence of hepatitis B virus infection. The management of HCC in Indonesia, as the world's largest archipelago with approximately 17,000 islands, is not easy. Only several centers in Indonesia have the resources needed for the management of HCC. Some patients from rural areas might need more than one month of referral process before they were able to get medical services in the referral hospitals. This long process together with the aggressive nature of liver cancer, finally made some patients become ineligible for definitive treatment.

Lastly, there has been no established surveillance system for HCC in our country until now. Most patients were already symptomatic when they were diagnosed with HCC. Therefore, large efforts should be made in the future in order to improve the outcome of HCC patients.

Despite some limitations of our study, this study may contribute to enrich data on HCC in Indonesia, especially regarding intermediate-stage HCC. We have tried to collect as much data as possible, but some data was still missing. This will be our next homework to encourage clinicians to complete the patients' database and to improve our electronic health record system.

CONCLUSION

Only 35.7% of patients with intermediate-stage HCC was treated with TACE as first-line treatment. An improvement in the treatment strategy should be done for HCC patients in Indonesia.

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