CANCER DIAGNOSIS & PROGNOSIS
4: 111-116 (2024) doi: 10.21873/cdp.10295

Systemic Chemotherapy for Advanced Hepatocellular Carcinoma in Patients With Child-Pugh class B

AKIFUMI KUWANO, MASAYOSHI YADA, KOSUKE TANAKA, YUTA KOGA, SHIGEHIRO NAGASAWA, AKIHIDE MASUMOTO and KENTA MOTOMURA

Department of Hepatology, Aso Iizuka Hospital, Fukuoka, Japan

Abstract. *Background/Aim: Numerous agents, including immune checkpoint inhibitors, are now available for hepatocellular carcinoma (HCC) treatment. Most trials involving systemic chemotherapy have included patients with Child-Pugh class A, while excluding or minimally enrolling those with Child-Pugh class B, due to liver dysfunction-related mortality. This study aimed to identify prognostic factors for survival in Child-Pugh class B patients receiving sorafenib (SOR), lenvatinib (LEN), atezolizumab plus bevacizumab (ATZ+BEV), or hepatic arterial infusion chemotherapy (HAIC). Patients and Methods: From December 2003 to June 2023, 137 patients with advanced HCC receiving systemic chemotherapies (SOR: n=43, LEN: n=16, ATZ+BEV: n=18, HAIC: n=60) were enrolled. Results: Overall survival (OS) and response rates did not differ significantly across treatments (SOR: 8.3 months, LEN: 10.2 months, ATZ+BEV: 8.5 months, HAIC: 7.3 months). Patients on HAIC and LEN had a lower rate of discontinuing treatment within three months compared to those on ATZ+BEV and SOR. HAIC was associated with fewer changes in ALBI score and better preservation of liver function. Multivariate logistic regression identified serum α-fetoprotein >400 ng/ml [hazard ratio (HR)=1.94; p=0.001], tumor count >5 (HR=1.55; p=0.043), and Child-Pugh score (HR=2.53; p=0.002) as independent predictors of OS. Conclusion: OS and response rates were similar across systemic chemotherapies. Prognosis for HCC in Child-Pugh class B patients was associated with liver function, necessitating further research for optimal treatment.*

Correspondence to: Masayoshi Yada, MD, Ph.D., Department of Hepatology, Aso Iizuka Hospital, 3-83 Yoshio-machi, Iizuka, Fukuoka 820-8505, Japan. Tel: +81 948223800, Fax: +81 948295744, e-mail: myadah1@aih-net.com

Key Words: Hepatocellular carcinoma, systemic chemotherapy, Child-Pugh class B.

Hepatocellular carcinoma (HCC) ranks as the sixth most prevalent malignancy and the third leading cause of cancer-induced mortality worldwide, with approximately 900,000 new cases and 830,000 fatalities in 2020 (1, 2). Effective treatments for advanced HCC did not emerge until 2007 (3). Prior to the advent of tyrosine kinase inhibitors, numerous clinical trials for drug therapies for unresectable HCC were conducted without any chemotherapeutic drugs demonstrating a survival benefit, as indicated by a meta-analysis by Mathurin *et al.* (4). Following research into tumor cell proliferation and angiogenesis mechanisms, the tyrosine kinase inhibitor Sorafenib (SOR) was developed (5). In the "SHARP trial" for unresectable HCC, SOR significantly improved survival over placebo, establishing it as the standard treatment for unresectable HCC in 2007 (6). In 2018, Lenvatinib (LEN) was found to be "non-inferior" to SOR in the "REFLECT trial", offering a choice between SOR or LEN as first-line therapy (7). The emergence of immune checkpoint inhibitors introduced a combination therapy of atezolizumab and bevacizumab (ATZ+BEV) in 2020, which outperformed SOR in clinical trials (8). Consequently, numerous agents, including immune checkpoint inhibitors, have become available for treating unresectable HCC. Hepatic arterial infusion chemotherapy (HAIC) is a localized treatment delivering cytotoxic chemotherapy directly into the hepatic artery *via* an implanted catheter port system, aiming to maximize HCC exposure to the chemotherapy while minimizing systemic side effects. HAIC has shown promising results in unresectable HCC patients (9). Liver function is assessed with the Child–Pugh classification, which ranges from Child–Pugh class A, indicative of compensated cirrhosis, to Child–Pugh class B and C, which signify decompensated cirrhosis (10). Most systemic chemotherapy

trials have enrolled patients with Child–Pugh class A status, often excluding or enrolling few patients with Child–Pugh class B due to the competing risk of mortality from liver dysfunction rather than HCC progression. Thus, systemic chemotherapy is generally recommended for HCC patients with Child-Pugh class A, while optimal treatments for patients with Child–Pugh class B have not been established. Here, our analysis evaluated the outcomes of Child–Pugh class B patients who received systemic chemotherapies (SOR, LEN, ATZ+BEV, HAIC) for HCC, aiming to identify prognostic survival factors.

Patients and Methods

Patients. In this prospective, single-center study at Aso Iizuka Hospital, the efficacy of systemic chemotherapy was evaluated from December 2003 to June 2023. Systemic chemotherapy treatments (SOR, LEN, ATZ+BEV, HAIC) were administered to 136 patients classified under Child-Pugh class B. The study, adhering to the Declaration of Helsinki, was sanctioned by the Ethics Committee of Aso Iizuka Hospital. Patient consent was obtained using the opt-out approach (approval code: 23139).

Assessment of liver function. Liver function was measured with the ALBI score, derived from the following formula: ALBI score = (log10(T-Bil[mg/dl]×17.1)×0.66) + ((ALB[g/dl]×10)×–0.085). In this formula, T-Bil signifies total bilirubin, and ALB represents the serum albumin level (11).

Chemotherapy regimens. SOR. SOR in doses ranging from 200-800 mg (Bayer Health Care Pharmaceuticals, West Haven, CT, USA), was administered according to package guidelines. Generally, the standard dose is 800mg/day, but initial dosing was tailored based on patient age, body weight, performance status, and liver function.

LEN. LEN was prescribed based on patient body weight (8 mg/day for those under 60 kg, or 12 mg/day for those weighing 60 kg or more) (Eisai Co., Ltd., Tokyo, Japan). We adjusted LEN dosages in response to LEN-induced adverse events, following the Common Terminology Criteria for Adverse Events, version 4.0. Doses were either reduced or temporarily discontinued until adverse event symptoms reduced to grade 1 or 2.

ATZ+BEV. Following the Imbrave150 trial guidelines (8), patients received intravenous doses of atezolizumab (1,200 mg) and bevacizumab (7.5 mg/kg) (Chugai Co., Ltd., Tokyo, Japan) every three weeks, continuing until either disease progression or the occurrence of intolerable side effects.

HAIC. A 5-Fr-W-spiral catheter (Piolax, Yokohama, Japan) was inserted *via* the right femoral artery for HAIC catheter implantation. The catheter's distal end was placed in the hepatic or gastroduodenal artery, and a subcutaneous port (Sofa Port, Nipro Pharma Co., Ltd., Osaka, Japan) was installed in the front femoral region (12). The HAIC treatment involved a cisplatin-lipiodol mixture, comprising 10-50 mg of finely powdered cisplatin in 5-10 ml of lipiodol, adjusted according to tumor size. On day one, this suspension was injected through the catheter under angiography, followed by a 5-day continuous infusion of 1500 mg 5-FU *via* an infusion balloon pump (SUREFUSER PUMP; Nipro Pharma Co., Ltd.).

Evaluation of efficacy. Treatment responses were evaluated every 6 to 12 weeks using either computed tomography or magnetic resonance imaging. The assessment of antitumor effects employed the Modified RECIST version 1.1 criteria (13). Indicators of the disease control rate (DCR) included complete response (CR), partial response (PR), and stable disease (SD) for a minimum of 4 months. The objective response rate (ORR) combined PR and CR. Patient evaluations and treatments were conducted every three weeks until either disease progression or unacceptable adverse effects occurred.

Statistical analysis. Statistical analysis was conducted using JMP Pro version 11 (SAS Institute, Cary, NC, USA), with results presented as medians. The Kaplan–Meier method, log-rank test, and Cox hazard analysis were applied for comparative statistical analyses. The chi-squared test or Fisher exact test assessed group differences, considering a p-value below 0.05 as significant.

Results

Patient characteristics. The characteristics of the 137 patients who underwent systemic chemotherapy are presented in Table I (SOR: n=43, LEN: n=16, ATZ+BEV: n=18, HAIC: n=60). Patients who underwent HAIC were younger than those who received other treatments. Patients treated with ATZ+BEV had a higher incidence of microvascular invasion (MVI) positivity, while those treated with HAIC had a higher incidence of extrahepatic spread (EHS) positivity and larger tumor sizes than those receiving other treatments. Patients receiving ATZ+BEV or HAIC had poorer Child–Pugh scores compared to those treated with SOR or LEN. Patients undergoing HAIC treatment were more likely to have BCLC stage C HCC. Serum α-fetoprotein (AFP) levels were lower in patients treated with LEN compared to other therapies. Sex, albumin-bilirubin (ALBI) scores, the number of intrahepatic lesions, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels were similar across the different treatments.

Overall survival (OS). No significant differences in OS were observed among the different systemic chemotherapy groups (SOR: 8.3 months, LEN: 10.2 months, ATZ+BEV: 8.5 months, HAIC: 7.3 months) (Figure 1).

Overall response. The ORR among patients who received SOR was 4/43 (12.1%), and the DCR was 6/43 (18.2%). The ORR for patients who received LEN was 2/16 (12.5%) and the DCR was 8/16 (50.0%). For those who received ATZ+BEV, the ORR was 2/18 (15.4%) and the DCR was 8/18 (61.5%). For patients treated with HAIC, the ORR was 17/60 (29.8%) and the DCR was 26/60 (45.6%). There were no significant differences in ORR among the systemic chemotherapy treatments (Table II).

Table I. *Baseline characteristics of patients who received systemic chemotherapies.*

Characteristics	SOR	LEN	ATZ+BEV	HAIC	*p*-Value
Number	43	16	18	60	
Age, years	70.37±9.24	75.56±6.51	72.80±8.04	64.81±10.61	0.0001
Sex, n (male/female)	36/7	11/5	13/5	47/13	0.5836
MVI positive, n	13	4	5	27	0.2487
EHS positive, n	19	5	2	26	0.0397
Intrahepatic max tumor size, cm	3.32±2.49	4.17±3.15	4.52±2.85	5.51±3.19	0.0010
Numbers of tumors >5	25	7	11	43	0.4525
Etiology					0.3021
HBV	6	4	3	17	
HCV	27	6	10	36	
NBNC	10	6	5	7	
Child-Pugh score 7/8/9	32/7/4	13/2/1	7/6/5	31/23/6	0.0211
Alb, g/dl	2.94±0.42	3.06±0.39	2.81±0.45	2.86±0.41	0.1698
T.Bil, g/dl	1.34±0.96	1.35±0.54	1.46±0.96	1.33±0.78	0.7426
ALBI score	–1.66±0.39	–1.72±0.27	–1.51±0.37	–1.58±0.39	0.2945
BCLC stage					0.0046
A	0	2	1	0	
B	18	8	10	14	
C	25	6	7	46	
Tumor marker					
AFP, ng/ml	7,543.53±39,228.54	611.59±1,383.16	5,496.00±13,891.80	37,209.12±130,397.43	0.0089
PIVKA-II, mAU/ml	17,709.59±88,113.09	13977.38±40,927.16	7078.35±10,756.81	11,660.59±28,185.83	0.1861

Data are expressed as median. SOR: Sorafenib; LEN: lenvatinib; ATZ+BEV: atezolizumab plus bevacizumab; HAIC: hepatic arterial infusion chemotherapy; HBV: hepatitis B virus; HCV: hepatitis C virus; MVI: microvascular invasion; EHS: extrahepatic spread; Alb: albumin; T.Bil: total bilirubin; ALBI score: albumin-bilirubin score; BCLC stage: Barcelona Clinic liver cancer stage; AFP: α-fetoprotein; PIVKA-II: vitamin K absence or antagonist-II.

Rate of treatment discontinuation and effects on liver function. Patients receiving HAIC and LEN were less likely to discontinue treatment within 3 months compared to those receiving ATZ+BEV and SOR (Table III). HAIC treatment resulted in fewer ALBI score changes and better preserved liver function (Figure 2).

Factors associated with OS. Univariate analysis revealed that a tumor number >5, Child-Pugh score, and serum AFP >400 ng/ml were associated with OS. The type of systemic chemotherapy regimen did not affect the OS of advanced HCC patients with Child-Pugh class B. Multivariate analysis identified serum AFP >400 ng/ml [hazard ratio (HR)=1.94; p=0.001], tumor number >5 (HR=1.55; p=0.043), and Child-Pugh score (HR=2.53; p=0.002) as independent factors associated with OS.

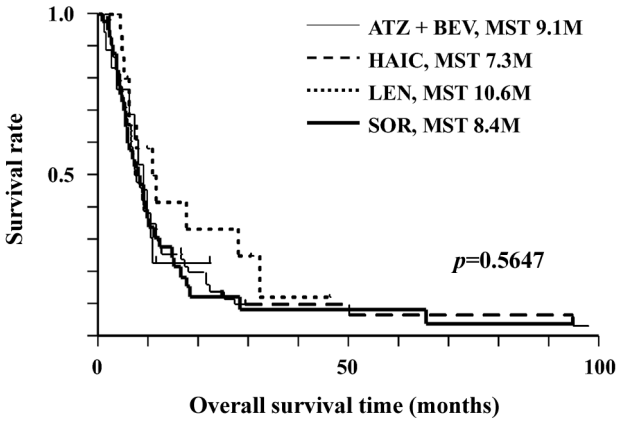

Figure 1. *Kaplan–Meier estimates of over survival (OS) in patients treated with systemic chemotherapies. Significant differences in OS were determined using the log-rank test. Time 0 was defined as the date of administration of systemic chemotherapies. SOF: Sorafenib; LEN: lenvatinib; ATZ+BEV: atezolizumab plus bevacizumab; HAIC: hepatic arterial infusion chemotherapy.*

Discussion

The effectiveness of systemic chemotherapies in patients with Child-Pugh class B remains uncertain, as these patients have been historically excluded from clinical trials of anticancer drugs. Currently, there is no established treatment for advanced HCC patients with Child–Pugh class B. This study is the first to compare SOR, LEN, ATZ+BEV, and HAIC in unresectable HCC patients with Child-Pugh class B. The GIDEON study was a prospective, observational registry designed to evaluate the real-world safety of SOR in patients with HCC. It included data from 669 treatment-naive patients with Child-Pugh class

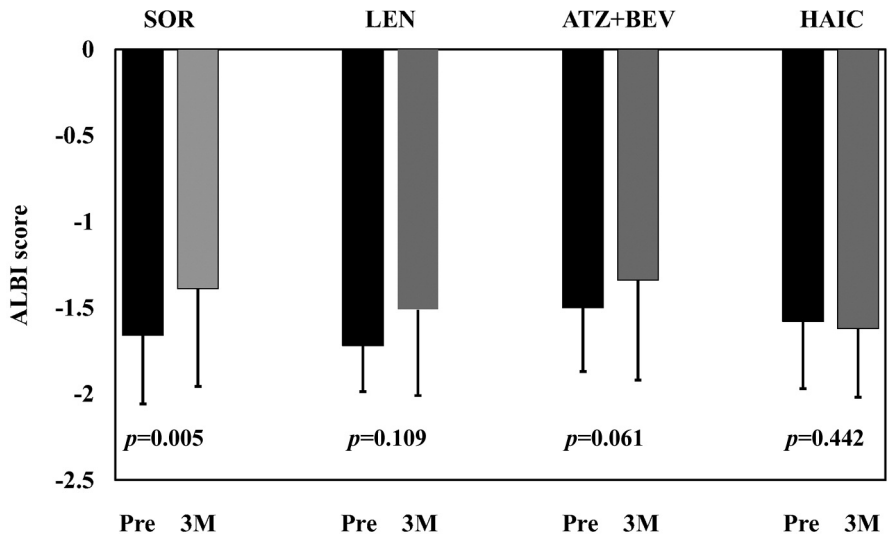

Figure 2. *The effect of systemic chemotherapies on liver function. ALBI: Albumin-bilirubin; SOF: sorafenib; LEN: lenvatinib; ATZ+BEV: atezolizumab plus bevacizumab; HAIC: hepatic arterial infusion chemotherapy.*

Table II. *Comparison of responses to systemic chemotherapies.*

	SOR	LEN	ATZ+BEV	HAIC	*p*-Value
Overall response					0.0010
CR	0	0	0	4	
PR	4	2	2	13	
SD	2	6	6	9	
PD	27	8	5	31	
NE	10	0	5	3	
ORR (CR+PR)	4 (12.1%)	2 (12.5%)	2 (15.4%)	17 (29.8%)	0.1521
DCR (CR+PR+SD)	6 (18.2%)	8 (50.0%)	8 (61.5%)	26 (45.6%)	0.0153

SOR: Sorafenib; LEN: lenvatinib; ATZ+BEV: atezolizumab plus bevacizumab; HAIC: hepatic arterial infusion chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

B. The median OS was significantly shorter for patients with Child-Pugh class B compared to those with Child-Pugh class A. Similarly, higher adverse event rates were observed in patients with Child-Pugh class B (14). Studies have demonstrated lower response rates and shorter OS in patients with HCC treated with LEN who had Child-Pugh class B compared to those with Child-Pugh A class (15, 16). Several studies reported that patients with HCC treated with atezolizumab and bevacizumab showed a significant difference in median OS between Child-Pugh class A and B (17, 18). It has been reported that OS did not significantly differ between patients with Child-Pugh class A and B who received HAIC (19). This study also indicated that HAIC treatment resulted in lower treatment discontinuation rates and fewer ALBI score changes. Most patients in our study with HCC who received HAIC had active hepatitis C virus (HCV) infection before the introduction of direct-acting antivirals. Previous reports have highlighted the crucial role of HCV eradication in the survival outcomes of advanced HCC patients treated with SOR (20). Given the historical context, HAIC may represent an important treatment option for HCC in

Table III. *Discontinued treatment within three months.*

	Discontinued treatment n (%)
SOR (n=43)	10 (23.3%)
LEN (n=16)	1 (6.3%)
ATZ+BEV (n=18)	7 (38.9%)
HAIC (n=60)	10 (16.7%)

SOR: Sorafenib; LEN: lenvatinib; ATZ+BEV: atezolizumab plus bevacizumab; HAIC: hepatic arterial infusion chemotherapy.

patients with Child-Pugh class B. There are few studies comparing various systemic chemotherapy treatments. Ohama *et al*. (21) found no significant differences in OS between Child-Pugh class B patients treated with ATZ+BEV and LEN. Kikugawa *et al*. (22) reported similar findings, adding that Child-Pugh score was an OS-associated factor, as observed in our study. This study's limitations include a small sample size and its single-center design. It encompasses unresectable HCC patients across different stages and eras. Ideally, the groups would be matched by liver function, HCC stage, and chemotherapy line, but this is challenging with a small cohort. The absence of a control group not receiving treatment also obscures the potential benefit of systemic chemotherapy for patients with Child-Pugh class B. Recent advances include the STRIDE regimen, combining Durvalumab and Tremelimumab, which surpassed SOR in the HIMALAYA trial, and Durvalumab monotherapy, which demonstrated non-inferiority to SOR (23). Kudo *et al*. noted the effectiveness and safety of Nivolumab, suggesting its suitability for patients with Child-Pugh class B (24). The use of Durvalumab and Tremelimumab promises efficacy and safety for such patients.

Conclusion

There were no significant differences in OS and response rates among the systemic chemotherapies. The prognosis for HCC patients with Child-Pugh class B was linked to liver function. Further research is required to determine optimal treatments for HCC in patients with Child-Pugh class B.

Conflicts of Interest

All Authors declare no competing interests in relation to this study.

Authors' Contributions

A.K., M.Y., A.M., and K.M. designed the study. A.K., Y.K, S.N., K.T., and M.Y. assisted with the data analyses. A.K. wrote the initial draft of the manuscript. M.Y. contributed to the analysis and interpretation of the data. M.Y., A.M., and K.M. assisted in the preparation and critical review of the manuscript. All Authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Acknowledgements

The Authors are grateful to Y. Ishibashi for his assistance with manuscript preparation.

References

1 Caldwell S, Park SH: The epidemiology of hepatocellular cancer: from the perspectives of public health problem to tumor biology. J Gastroenterol 44(S19): 96-101, 2009. DOI: 10.1007/s00535-008-2258-6

2 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3): 209-249, 2021. DOI: 10.3322/caac.21660

3 Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS: Hepatocellular carcinoma. Nat Rev Dis Primers 7(1): 6, 2021. DOI: 10.1038/s41572-020-00240-3

4 Mathurin P, Rixe O, Carbonell N, Bernard B, Cluzel P, Bellin MF, Khayat D, Opolon P, Poynard T: Overview of medical treatments in unresectable hepatocellular carcinoma-an impossible meta-analysis? Aliment Pharmacol Ther 12: 111-126, 1998. DOI: 10.1046/j.1365-2036.1998.00286.x

5 Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA: BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 64(19): 7099-7109, 2004. DOI: 10.1158/0008-5472.CAN-04-1443

6 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J, SHARP Investigators Study Group: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359(4): 378-390, 2008. DOI: 10.1056/NEJMoa0708857

7 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 391(10126): 1163-1173, 2018. DOI: 10.1016/S0140-6736(18)30207-1

8 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL, IMbrave150 Investigators: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382(20): 1894-1905, 2020. DOI: 10.1056/NEJMoa1915745

9 Kim HJ, Lee SH, Shim HJ, Bang HJ, Cho SH, Chung IJ, Hwang EC, Hwang JE, Bae WK: Hepatic arterial infusion chemotherapy versus systemic therapy for advanced hepatocellular carcinoma: a systematic review and meta-analysis. Front Oncol 13: 1265240, 2023. DOI: 10.3389/fonc.2023.1265240

10 Rivard C, Esnaola S, Villeneuve JP: Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. Hepatology 7(4): 660-664, 1987. DOI: 10.1002/hep.1840070408

11 Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, O'Beirne J, Fox R, Skowronska A, Palmer D, Yeo W, Mo F, Lai P, Iñarrairaegui M, Chan SL, Sangro B, Miksad R, Tada T, Kumada T, Toyoda H: Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 33(6): 550-558, 2015. DOI: 10.1200/JCO.2014.57.9151

12 Niizeki T, Iwamoto H, Shirono T, Shimose S, Nakano M, Okamura S, Noda Y, Kamachi N, Hiroyuki S, Sakai M, Kuromatsu R, Koga H, Torimura T: Clinical importance of regimens in hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with macrovascular invasion. Cancers (Basel) 13(17): 4450, 2021. DOI: 10.3390/cancers13174450
13 Lencioni R, Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30(01): 052-060, 2010. DOI: 10.1055/s-0030-1247132
14 Marrero JA, Kudo M, Venook AP, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JH, de Guevara LL, Papandreou C, Takayama T, Sanyal AJ, Yoon SK, Nakajima K, Lehr R, Heldner S, Lencioni R: Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol 65(6): 1140-1147, 2016. DOI: 10.1016/j.jhep.2016.07.020
15 Ogushi K, Chuma M, Uojima H, Hidaka H, Numata K, Kobayashi S, Hirose S, Hattori N, Fujikawa T, Nakazawa T, Wada N, Iwasaki S, Fukushima T, Sano Y, Ueno M, Kawano K, Tsuruya K, Shomura M, Watanabe T, Matsunaga K, Kunishi Y, Saigusa Y, Irie K, Iwabuchi S, Kako M, Morimoto M, Kagawa T, Tanaka K, Maeda S: Safety and efficacy of lenvatinib treatment in Child-Pugh A and B patients with unresectable hepatocellular carcinoma in clinical practice: a multicenter analysis. Clin Exp Gastroenterol 13: 385-396, 2020. DOI: 10.2147/CEG.S256691
16 Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, Takaguchi K, Kariyama K, Itobayashi E, Tajiri K, Shimada N, Shibata H, Ochi H, Tada T, Toyoda H, Nouso K, Tsutsui A, Nagano T, Itokawa N, Hayama K, Imai M, Joko K, Koizumi Y, Hiasa Y, Michitaka K, Kudo M, Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan): Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions-Multicenter analysis. Cancer Med 8(8): 3719-3728, 2019. DOI: 10.1002/cam4.2241
17 D'Alessio A, Fulgenzi CAM, Nishida N, Schönlein M, von Felden J, Schulze K, Wege H, Gaillard VE, Saeed A, Wietharn B, Hildebrand H, Wu L, Ang C, Marron TU, Weinmann A, Galle PR, Bettinger D, Bengsch B, Vogel A, Balcar L, Scheiner B, Lee PC, Huang YH, Amara S, Muzaffar M, Naqash AR, Cammarota A, Personeni N, Pressiani T, Sharma R, Pinter M, Cortellini A, Kudo M, Rimassa L, Pinato DJ: Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: A real-world study. Hepatology 76(4): 1000-1012, 2022. DOI: 10.1002/hep.32468
18 Muto H, Kuzuya T, Kawabe N, Ohno E, Funasaka K, Nagasaka M, Nakagawa Y, Miyahara R, Shibata T, Hashimoto S, Katano Y, Hirooka Y: Clinical outcomes with lenvatinib in patients previously treated with atezolizumab/bevacizumab for advanced hepatocellular carcinoma. Anticancer Res 43(10): 4673-4682, 2023. DOI: 10.21873/anticanres.16663
19 Ishii M, Itano O, Iwamoto H, Hibi T, Itano S: Efficacy and safety of arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma and Child-Pugh Class B: a retrospective cohort study. Oncology 100(5): 278-289, 2022. DOI: 10.1159/000523703
20 Kuwano A, Yada M, Nagasawa S, Tanaka K, Morita Y, Masumoto A, Motomura K: Hepatitis C virus eradication ameliorates the prognosis of advanced hepatocellular carcinoma treated with sorafenib. J Viral Hepat 29(7): 543-550, 2022. DOI: 10.1111/jvh.13681
21 Ohama H, Hiraoka A, Tada T, Hirooka M, Kariyama K, Tani J, Atsukawa M, Takaguchi K, Itobayashi E, Fukunishi S, Tsuji K, Ishikawa T, Tajiri K, Ochi H, Yasuda S, Toyoda H, Ogawa C, Nishimura T, Hatanaka T, Kakizaki S, Shimada N, Kawata K, Naganuma A, Kosaka H, Matono T, Shibata H, Aoki T, Tada F, Nouso K, Morishita A, Tsutsui A, Nagano T, Itokawa N, Okubo T, Arai T, Imai M, Koizumi Y, Nakamura S, Iijima H, Kaibori M, Hiasa Y, Kudo M, Kumada T, Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan): Comparison between atezolizumab plus bevacizumab and lenvatinib for hepatocellular carcinoma in patients with Child-Pugh class B in real-world clinical settings. Oncology 101(9): 542-552, 2023. DOI: 10.1159/000530028
22 Kikugawa C, Uchikawa S, Kawaoka T, Kinami T, Yano S, Amioka K, Naruto K, Ando Y, Yamaoka K, Tsuge M, Kosaka Y, Ohya K, Mori N, Takaki S, Tsuji K, Kouno H, Kohno H, Morio K, Moriya T, Nonaka M, Aisaka Y, Masaki K, Honda Y, Naeshiro N, Hiramatsu A, Aikata H, Oka S: Outcomes of patients with Child-Pugh B and unresectable hepatocellular carcinoma undergoing first-line systemic treatment with sorafenib, lenvatinib, or atezolizumab plus bevacizumab. Oncology: 1-13, 2023. DOI: 10.1159/000533859
23 Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, Sukeepaisarnjaroen W, Kang YK, Van Dao T, De Toni EN, Rimassa L, Breder V, Vasilyev A, Heurgué A, Tam VC, Mody K, Thungappa SC, Ostapenko Y, Yau T, Azevedo S, Varela M, Chrng AL, Qin S, Galle PR, Ali S, Marcovitz M, Makowsky M, He P, Kurland JF, Negro A, Sangro B: Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evidence 1(8), 2022. DOI: 10.1056/EVIDoa2100070
24 Kudo M, Matilla A, Santoro A, Melero I, Gracián AC, Acosta-Rivera M, Choo SP, El-Khoueiry AB, Kuromatsu R, El-Rayes B, Numata K, Itoh Y, Di Costanzo F, Crysler O, Reig M, Shen Y, Neely J, Tschaika M, Wisniewski T, Sangro B: CheckMate 040 cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. J Hepatol 75(3): 600-609, 2021. DOI: 10.1016/j.jhep.2021.04.047

Received November 21, 2023
Revised December 18, 2023
Accepted December 19, 2023