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Review

Clinical Benefits of Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma

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Abstract: Recent success of systemic therapeutic agents, including combination immunotherapy, could promote a change in the treatment strategy in patients with advanced hepatocellular carcinoma (HCC). Although hepatic arterial infusion chemotherapy (HAIC) is a treatment option for advanced HCC in Japan, it is not recommended by other guidelines. We discuss the clinical benefits of HAIC compared to sorafenib. The clinical benefits of HAIC are as follows: (1) even a patient with Child–Pugh B HCC (7 or 8 points) is a candidate for HAIC (2) Child–Pugh scores barely decline with the use of HAIC compared with sorafenib (3) HAIC is highly effective in patients with vascular invasion compared with sorafenib; and (4) survival in patients receiving HAIC may not be associated with skeletal muscle volume. In contrast, the disadvantages are problems related with the reservoir system. HAIC has clinical benefits in a subpopulation of patients without extrahepatic metastasis with Child–Pugh A HCC and vascular invasion (especially primary branch invasion or main portal vein invasion) or with Child–Pugh B HCC.

Keywords: advanced hepatocellular carcinoma; hepatic arterial infusion chemotherapy; sorafenib; vascular invasion

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1. Introduction

The introduction of sorafenib, a molecular-targeted agent (MTA), in 2007, has been a landmark in the history of systemic therapy for advanced hepatocellular carcinoma (HCC). After the success of the SHARP and Asia-Pacific trials [1,2], several clinical trials of new MTAs (e.g., sunitinib, brivanib, and linifanib, among others) conducted from 2007 until 2016 have failed [3,4]. However, the recent success of treatments in clinical trials, such as regorafenib, lenvatinib, cabozantinib, and ramucirumab, has changed the treatment strategy for advanced HCC [5–8]. Furthermore, the combination of atezolizumab with bevacizumab improved overall and progression-free survival outcomes compared with sorafenib in patients with advanced HCC [9]. This combination therapy was approved for unresectable HCC in clinical practice in the United States (US) and Japan in May 2020 and September 2020, respectively. Therefore, combination therapy is likely considered the first-line therapy for advanced HCC, and current first-line MTAs (sorafenib and lenvatinib) and second-line MTAs (regorafenib, ramucirumab, and cabozantinib) are likely to be

shifted to second- and third-line therapies, respectively [10]. However, as these above-mentioned drugs have been recommended to HCC patients with preserved liver, those with deteriorated liver function are generally not candidates for such drugs.

In contrast, hepatic arterial infusion chemotherapy (HAIC), which has been performed since the 1990s in Japan, may be a candidate for addressing an unmet medical need. Although several studies showed the efficacy of HAIC in a subpopulation of patients with advanced HCC [11–17], various guidelines from Asia, Europe, and the US do not recommend HAIC as a treatment option for advanced HCC due to low evidence levels, except for the Japanese guideline [18–21]. In addition, technical difficulties and medical care are needed to institute and maintain the reservoir system. Therefore, although HAIC has been used in East Asia, especially Japan, it has low feasibility as a treatment. Sorafenib has been widely used as a standard systemic therapeutic agent for more than 10 years, whereas adoption of HAIC has been limited. In this review, we discuss the current status and clinical benefits of HAIC for advanced HCC compared with sorafenib, based on articles published between 2008 and 2020.

2. Overview of HAIC

2.1. Concept

HAIC involves two procedures as follows: as scheduled, chemotherapeutic regimens are administered through a reservoir port connected to a catheter, which is implanted under the skin, and a catheter is inserted each time without implantation of the reservoir port. As HAIC is expected to accumulate drug concentrations in the local liver and reduce systemic toxicity of anti-cancer drugs, it is considered to have a more favorable antitumor effect and less influence on other organs than systemic chemotherapy. However, currently, no randomized controlled trials (RCTs) have compared HAIC with systemic chemotherapy in a large number of HCC patients.

2.2. Regimens

As the anti-cancer drugs that can be used in HAIC differ across countries, it may be difficult to adopt these HAIC regimens. In Japan, three regimens have been used for HAIC treatment: 5-fluorouracil (5-FU) combined with low-dose cisplatin (CDDP) (low-dose FP) [22–24], 5-FU combined with interferon (FAIT) [25–28], and CDDP alone [29–31] (Table 1). The response rates (complete response [CR] + partial response [PR]/all patients) of the regimens comprising low-dose FP or FAIT and the CDDP regimen were approximately 30–40% and 20–30%, respectively. Recently, HAIC regimens comprising low-dose FP or CDDP alone have been generally used in Japan [32].

2.3. Indications

HAIC is commonly used to treat advanced HCC, whether naive or recurrent tumors. According to the Clinical Practice Guidelines for Hepatocellular Carcinoma (2017 version) established by the Japan Society of Hepatology (JSH) [21], HAIC or MTA is recommended as a second-line treatment in HCC patients with $\geq$4 nodules, without vascular invasion and extrahepatic metastasis (EHM); whereas transcatheter arterial chemoembolization (TACE), hepatectomy, HAIC, and MTA are recommended as first-line treatments in HCC patients with vascular invasion, without EHM. Furthermore, patients with Child–Pugh A or B HCC are candidates for HAIC [21]. In this regard, the guidelines from Korea and Taiwan demonstrated that HAIC may be considered an optional treatment in a subpopulation of patients [33,34].

2.4. Clinical Outcomes

As shown in Table 1, the median survival time (MST) was different based on the degree of vascular invasion. Radiological responders (CR or PR) show significantly longer survival than radiological non-responders (stable or progressive disease). A Japanese nationwide survey reported that the MST was significantly longer in patients who received

HAIC (n = 341, 14 months) than in those who did not receive active treatment (n = 341, 5.2 months) in a propensity score-matched analysis [23]. In Child–Pugh A or B HCC patients with portal vein tumor thrombus, the MST was similarly significantly longer in patients receiving HAIC (7.9 months) than in those without therapy (3.1 months) [23]. A recent report demonstrated that none of the HAIC regimens (low-dose FP, FAIT, and CDDP alone) had no effect on survival in patients with advanced HCC [11].

Table 1. Regimens of hepatic arterial infusion chemotherapy.

Authors [Reference]	Publishing Year	Regimens	Case Number	Vascular Invasion (%)	Response Rate (%)	Median Survival Time (Months)
Low-dose FP						
Saeki, et al. [22]	2015	Low-dose FP including the combination of LV/IV or IV plus IFN	90	ND	34.4	10.6
Nouso, et al. [23]	2013	CDDP+5FU	476	44.1	40.5	14.0 (341 patients)
Ueshima, et al. [24]	2010	Low-dose FP	52	80.8	38.5	15.9
FAIT						
Monden, et al. [25]	2012	IFNα, 5-FU	34	90.0	26.7	8.4
		Low-dose FP/CDDP	35	90.3	25.8	11.8
Yamashita, et al. [26]	2011	IFNα, CDDP, 5-FU	57	26.7	45.6	17.6
		IFNα, 5-FU	57	50.0	24.6	10.5
Nagano, et al. [27]	2011	IFNα, 5-FU	102	100.0	39.2	9.0
Obi, et al. [28]	2006	IFNα, 5-FU	116	100.0	52.0	6.9
CDDP						
Ikeda, et al. [29]	2013	CDDP powder (IA call)	25	100.0	28.0	7.6
Kim, et al. [30]	2011	CDDP	41	83.3	12.2	7.5
		CDDP, 5-FU	97		27.8	12.0
Yoshikawa, et al. [31]	2008	CDDP powder (IA call)	80	27.5	33.8	ND

ND, not described; Low-dose FP, low-dose 5-fluorouracil plus cisplatin; LV, leucovorin; IV, isovorin; IFN, interferon; CDDP, cisplatin; 5-FU, 5-fluorouracil.

3. HAIC Versus SORAFENIB

3.1. Clinical Response and Outcomes

As mentioned earlier, no RCTs have compared HAIC with sorafenib in a large number of patients with advanced HCC. A few retrospective studies have compared HAIC with sorafenib as well as one RCT with a small population [11–17] (Table 2). The previous prospective and retrospective studies showed that the overall survival (OS) and response rate of HAIC were significantly higher than those of sorafenib in HCC patients with vascular invasion [12,14–16], and other studies indicated that the progression-free survival of HAIC was better than that of sorafenib [13,17]. However, these studies had small sample sizes. A recent retrospective cohort study with a large population (2006 patients: 541 patients with HAIC; 1465 patients with sorafenib) demonstrated that the MST of patients with vascular invasion without EHM was significantly longer in the HAIC group than in the sorafenib group (10.1 versus 9.1 months) after propensity score matching, although no significant difference in OS was observed between both groups in patients without both vascular invasion and EHM after propensity score matching (12.2 and 15.4 months for the HAIC and sorafenib groups, respectively) [11]. Similarly, a meta-analysis indicated that HAIC is superior to sorafenib in HCC patients with vascular invasion [35]. Furthermore,

Hatooka et al. reported that HAIC showed worse OS than sorafenib in the treatment of patients with HCC refractory to TACE [36]. Therefore, HAIC may be a potential first-line treatment in advanced HCC refractory to TACE with vascular invasion and without EHM.

Although sorafenib was introduced more than 10 years ago, the long-term survival at 10 years has not been established in a large number of patients with advanced HCC who received sorafenib. Rimola et al. reported that the CR rate and MST for CR patients receiving sorafenib were 1% (12 of 1119 patients) and 85.8 months, respectively [37]. In contrast, a Japanese nationwide follow-up survey indicated that the survival rate at 10 years was 5.0% in Child–Pugh A HCC patients treated with HAIC using a reservoir port [32]. Similarly, we showed that three of six CR patients who received HAIC using a low-dose FP-based regimen survived for over 10 years [38]. Further studies with a large sample size are necessary to compare long-term survival between the two treatments.

3.2. RCTs Comparing Sorafenib Plus HAIC with Sorafenib

As sorafenib has shown a clinical benefit [1,2], the combination of sorafenib with HAIC would be expected to have a synergistic effect on clinical outcomes. Currently, three RCTs comparing sorafenib plus HAIC with sorafenib have been conducted [39–41] (Table 3). The SILIUS study, which compared sorafenib plus HAIC using CDDP + 5-FU with sorafenib, demonstrated a significant difference in the response rate; however, no significant difference in OS was observed between the two groups [40]. Nevertheless, subgroup analyses of this study showed that sorafenib plus HAIC showed a survival benefit in advanced HCC patients with main portal vein tumor thrombus (so-called main portal vein invasion [Vp4]) (MST, 1.4 vs. 6.5 months; hazard ratio [HR], 0.493; $p = 0.050$), no significant differences in OS was observed among patients with Vp0 or Vp1-3 between the sorafenib plus HAIC group and the sorafenib group (Vp0: 11.3 and 11.9 months, HR, 1.001, $p = 0.996$; Vp1-3: 12.6 and 14.4 months, HR, 1.367, $p = 0.423$, respectively). Other studies indicated that survival was significantly longer in the sorafenib plus HAIC group than in the sorafenib group [39,41]. Especially, subgroup analyses stratified by the grade of portal vein invasion showed similar results (Vp1-2: 18.17 vs. 10.87 months, HR, 0.33, $p = 0.002$; primary branch portal vein invasion [Vp3]: 13.47 vs. 6.27 months, HR, 0.29, $p < 0.001$; Vp4: 9.47 vs. 5.5 months, HR, 0.40, $p < 0.001$) [39]. Based on these reports, the combination of sorafenib and HAIC may be expected to have a survival benefit compared with sorafenib alone in advanced HCC with vascular invasion.

3.3. HAIC versus Sorafenib Based on Liver Function

For patients with HCC, preserving liver function during and after several treatments is extremely important to achieve positive long-term prognoses. MTAs, including sorafenib, are generally used in patients with Child–Pugh A HCC, whereas HAIC is administered in patients with Child–Pugh A or B HCC. Terashima et al. reported that the Child–Pugh scores at 4 and 12 weeks after HAIC did not significantly decline compared with those after sorafenib treatment among patients with Child–Pugh A HCC [42]. The Child–Pugh score of responders to HAIC with Child–Pugh B HCC was significantly improved, unlike that of non-responders [41]. In addition, patients with a Child–Pugh B of 7 or 8 points were candidates for HAIC, and the clinical benefit of HAIC was extremely limited for patients with a Child–Pugh B score of 9 points [43]. Similarly, our previous report demonstrated that among HAIC responders, the Child–Pugh class of most patients showed no decline after HAIC, and the Child–Pugh class significantly improved after HAIC among responders with Child–Pugh B HCC before HAIC [44].

Table 2. Summary of hepatic arterial infusion chemotherapy versus sorafenib.

Authors [Reference]	Publishing Year	Study Design	Regimens	Case Number	Vp3+Vp4 (%)	Response Rate (%)	Median Survival Time (Months)	Outcomes			
Ueshima, et al. [11]	2020	Retrospective cohort study	HAIC using several regimens	541	41.2 (Vp3, Vp4, Vv3, or B4)	ND	10.1 (cohort 1) 12.2 (cohort 2)	OS (cohort 1; MVI+, EHM-)	HAIC > SOR	$p = 0.018$	after PSM (n = 170 for each)
			Sorafenib	1465	17.1 (Vp3, Vp4, Vv3, or B4)	ND	9.1 (cohort 1) 15.4 (cohort 2)	OS (cohort 2; MVI-, EHM-)	Not significant	$p = 0.475$	after PSM (n = 76 for each)
Choi, et al. [12]	2018	RCT	HAIC using CDDP + 5-FU	29	100.0	27.6	14.9	OS	HAIC > SOR	$p = 0.012$	
			Sorafenib	29	100.0	3.4	7.2	TTP	HAIC > SOR	$p = 0.010$	4.4 vs. 2.7 months
Kang, et al. [13]	2018	Retrospective cohort study	HAIC using CDDP + 5-FU	95	76.8 (PVTT) ND (Vp3+Vp4)	23.2	12.0	OS	Not significant	$p = 0.050$	
			Sorafenib	44	61.4 (PVTT) ND (Vp3+Vp4)	2.3	7.4	PFS	HAIC > SOR	$p = 0.030$	9.1 vs. 5.5 months
Moriguchi, et al. [14]	2017	Retrospective cohort study	HAIC using CDDP + 5-FU	32	100.0	31.3	10.3	OS	HAIC > SOR	$p = 0.009$	
			Sorafenib	14	100.0	0.0	4.0	TTP	HAIC > SOR	$p = 0.022$	3.6 vs. 1.2 months
Song, et al. [15]	2015	Retrospective cohort stud	HAIC using CDDP + 5-FU	50	86.0	24.0	7.2	OS	HAIC > SOR	$p = 0.011$	
			Sorafenib	60	91.7	13.3	5.5	TTP	HAIC > SOR	$p = 0.034$	3.3 vs. 2.1 months
Kawaoka, et al. [16]	2015	Retrospective cohort study	HAIC using CDDP + 5-FU or 5FU + IFN	136	46.3	30.9	10.0	OS in patients with MVI	HAIC > SOR	$p = 0.018$	after the case–control method (n = 16 for each)
			Sorafenib	41	29.3	4.8	10.0				
Fukubayashi, et al. [17]	2015	Retrospective cohort study	HAIC using CDDP + 5-FU or 5FU + IFN	128	50.0 (PVTT) ND (Vp3+Vp4)	26.6	8.8	OS PFS	Not significant	$p = 0.750$ $p = 0.090$	after PSM (n = 53 for each)
			Sorafenib	72	70.8 (PVTT) ND (Vp3+Vp4)	15.3	12.5	PFS in patients with PVTT	HAIC > SOR	$p = 0.008$	after P SM (n = 25 for HAIC, n = 20 for SOR)

Vp3, primary branch portal vein invasion; Vp4, main portal vein invasion; MVI, microvascular invasion; Vv3, inferior vena cava invasion; HAIC, hepatic arterial infusion chemotherapy; ND, not described; OS, overall survival; EHM, extrahepatic metastasis; SOR, sorafenib; PSM, propensity score matching; RCT, randomized controlled trial; CDDP, cisplatin; 5-FU, 5-fluorouracil; TTP, time to progression; PFS, progression-free survival; PVTT, portal vein tumor thrombosis.

Table 3. Randomized controlled trials comparing sorafenib plus hepatic arterial infusion chemotherapy with sorafenib.

Authors [Reference]	Publishing Year	Study Design	Indication	Regimens	Case Number	Response Rate (%)	*p* Value for Response	Median Survival Time (Months)	HR and *p* Value for OS
He, et al. [39]	2019	RCT phase III	BCLC stage C with portal vein invasion	Sorafenib plus HAIC using oxaliplatin, 5-FU, and leucovorin (FOLFOX)	125	40.8	$p < 0.010$	13.37	HR, 0.35 (0.26-0.48) $p < 0.001$
				Sorafenib	122	2.46		7.1	
Kudo, et al. [40]	2018	RCT phase III (SILIUS)	BCLC stage B/C and Child–Pugh A/B (7 pts)	Sorafenib plus HAIC using CDDP and 5-FU	102	36.5	$p < 0.010$	11.8	HR, 1.009 (0.743-1.371) $p = 0.955$
				Sorafenib	103	17.5		11.5	
Ikeda, et al. [41]	2016	RCT phase II	BCLC stage B/C and Child–Pugh A	Sorafenib plus HAIC using CDDP	66	21.7	$p = 0.090$	10.6	HR, 0.60 (0.38-0.96) $p = 0.031$
				Sorafenib	42	7.3		8.7	

HR, hazard ratio; OS, overall survival; RCT, randomized controlled trial; BCLC, Barcelona Clinic Liver Cancer; HAIC, hepatic arterial infusion chemotherapy; 5-FU, 5-fluorouracil; CDDP, cisplatin.

3.4. HAIC versus Sorafenib Based on Sarcopenia

Sarcopenia has been defined as the loss of skeletal muscle mass, physical performance (e.g., walking speed), and strength according to the European Working Group on Sarcopenia in older People and the Asian Working Group for Sarcopenia [45,46]. In contrast, the JSH proposed a diagnostic criterion for sarcopenia in patients with chronic liver disease of "loss of muscle mass plus low muscle strength" [47]. However, in previous reports, skeletal muscle depletion has been commonly used as the definition for sarcopenia in patients with HCC [48,49]. Previous studies analyzing HCC patients who received sorafenib demonstrated that skeletal muscle depletion was almost associated with poor prognosis [48–53]. Similarly, it has been reported that skeletal muscle depletion was a poor prognostic factor in patients with HCC treated with lenvatinib [54]. Furthermore, it is important to investigate skeletal muscle change during MTA use. The annual rates of skeletal muscle volume decline in cirrhotic patients without HCC were reported to be 1.3%, 3.5%, and 6.1% for Child–Pugh class A, B, and C, respectively [55]. Conversely, our previous study showed that skeletal muscle mass decreased by 5.5% at 3 months after starting sorafenib [53], and another report indicated that treatment with sorafenib or lenvatinib showed a significant depletion of skeletal muscle volume regardless of disease progression and hepatic reserve function [56]. In the era of MTAs, sequential therapy using MTAs may decrease skeletal muscle volume markedly higher than a first-line MTA therapy. Currently, there have been no reports regarding the relationship between sarcopenia and clinical outcomes in patients treated with atezolizumab plus bevacizumab and other MTAs, except for sorafenib and lenvatinib.

This is the first study demonstrating that skeletal muscle depletion is not associated with OS in patients with HCC treated with HAIC compared with sorafenib [57]. As there have been no similar reports, this finding will need to be validated. Thus, the different results related to skeletal muscle mass between HAIC and sorafenib may be worthy of notice when considering the use of treatment modalities for advanced HCC.

3.5. Sequential Therapy: HAIC Followed by Sorafenib versus Sorafenib Followed by HAIC

The RESORCE study and a sub-analysis of the REFLECT study demonstrated that sequential therapy improved survival in patients who were refractory to the first-line therapy [5,58]. Post-progression survival (PPS) is an important factor for prolonging OS. Our previous reports showed that post-treatment after HAIC failure was a significant independent predictor of OS before the development of MTAs [59,60]. Retrospective cohort studies, including the present study, demonstrated that conversion to sorafenib after HAIC failure was a significant prognostic factor [57,61]. However, as these studies had small sample sizes, large comparative studies are necessary to confirm the survival benefit of this sequential therapy.

In contrast, it has been reported that subsequent therapy, including TACE and HAIC, contributed to prolonging PPS after sorafenib failure [62–64]. However, the sequential therapies administered after sorafenib failure were heterogeneous. To our knowledge, there have been no reports comparing between patients who received only HAIC and those who did not receive any subsequent therapy. As it is difficult to perform a prospective study of subsequent therapy using HAIC versus no therapy, propensity score matching will be needed to evaluate this finding.

4. Clinical Benefits and Disadvantages of HAIC

The clinical benefits of HAIC for advanced HCC are as follows: (1) even a patient with Child–Pugh B HCC (7 or 8 points) is a candidate for HAIC [43], (2) Child–Pugh scores barely decline after HAIC [42,44], (3) HAIC is highly effective in patients with vascular invasion compared with sorafenib [11,35], and 4) survival in patients receiving HAIC may not be associated with skeletal muscle volume [57]. In contrast, the disadvantages of HAIC for advanced HCC are as follows: (1) a highly technical procedure is needed to implant a catheter with a reservoir port; (2) hospitalization is needed to continue HAIC treatments; (3)

patients have to return for follow-up visits every 2 weeks to maintain the reservoir system; and (4) adverse events related to the reservoir system, such as port migration, catheter dislocation, arterial occlusion, reservoir system occlusion, subcutaneous hematomas, or infection [65].

Atezolizumab combined with bevacizumab was recently approved, and this combination will be recommended as the first-line therapy for advanced HCC. However, a comparison between atezolizumab plus bevacizumab and HAIC has not been performed. Patients with macrovascular invasion, including an invasion of the main portal trunk, accounted for 38% of those in the atezolizumab plus bevacizumab group; however, the details were not shown [9]. Therefore, as there has been no information regarding this combination therapy in real-world practice, further studies are required.

We present a draft of the treatment proposal for HAIC for advanced HCC in Figure 1. The combination of atezolizumab and bevacizumab will be shifted to the first-line therapy in patients with Child–Pugh A HCC, regardless of EHM, and currently used MTAs will be shifted to later lines of therapy [10]. HAIC may be an optional treatment in patients with Child–Pugh A HCC and vascular invasion, especially Vp3 or Vp4, without EHM [11,35]. MTAs are generally used in patients with Child–Pugh A HCC, whereas the use of MTAs in patients with Child–Pugh B HCC remains controversial. Some Asian guidelines recommended that sorafenib is considered in selected patients with Child–Pugh B (e.g., score, 7 points) [18,33,34,66,67], although sorafenib treatment significantly worsened survival in patients with Child–Pugh B HCC compared to those with Child–Pugh A HCC [68]. In contrast, patients with Child–Pugh B HCC (score 7 or 8 points) are candidates for HAIC [43]. The medical needs of patients receiving second-line therapy for Child–Pugh B HCC without EHM and those who have EHM with Child–Pugh B HCC, are yet to be met. However, HAIC may be considered in a subpopulation of both Child–Pugh B HCC and EHM patients if the intrahepatic tumor is directly linked to prognosis. Therefore, patients in clinical trials who can tolerate deteriorated liver function would be candidates for the novel therapy [69,70]. We have reported the efficacy of arterial infusion of an iron chelator, deferoxamine, which is not an anti-cancer drug but is used for treating iron overload disease in advanced HCC patients, including Child–Pugh B or C patients [69]. However, deferasirox, an oral iron chelator, has limited efficacy due to associated adverse effects, especially renal dysfunction [70]. In the future, systemic therapeutic agents would be expected to be developed for the unmet medical needs of patients undergoing advanced HCC treatment.

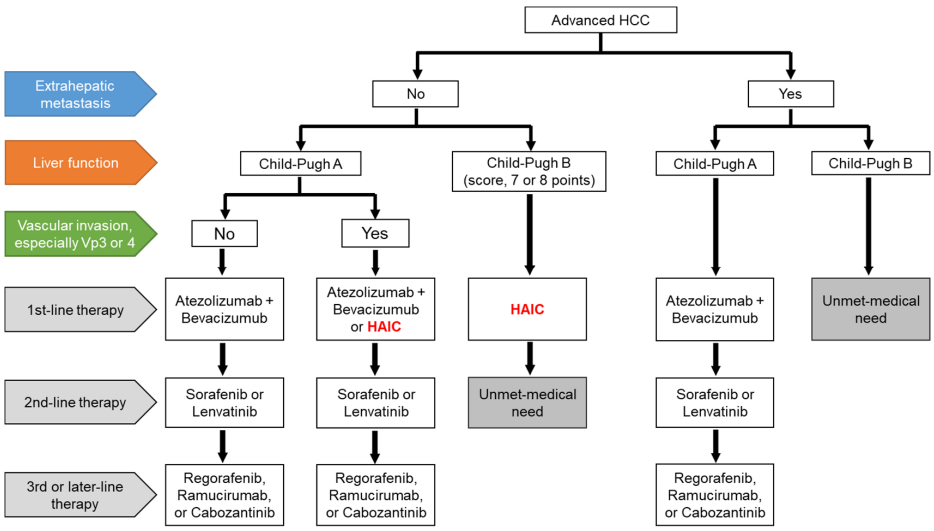

Figure 1. A draft of the treatment proposal for advanced HCC. HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; Vp3, primary branch portal vein invasion; Vp4, main portal vein invasion.

5. Conclusions

Although HAIC was not recommended as a treatment option for advanced HCC by various guidelines, several studies demonstrated that HAIC has clinical benefits in a subpopulation of patients with advanced HCC, such as Child–Pugh A HCC with primary branch/main portal vein invasion without EHM and Child–Pugh B HCC without EHM. In fact, HAIC is currently the only treatment option to address the unmet medical needs of Child–Pugh B HCC patients. In the future, HAIC may be recommended as a treatment for advanced HCC if it is widely adopted and a large body of supporting evidence is generated.

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