Hepatic arterial infusion chemotherapy and sequential ablation treatment in large hepatocellular carcinoma

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ABSTRACT

Aim: To investigate the individualized survival benefit of hepatic arterial infusion chemotherapy (HAIC) and sequential ablation treatment in large hepatocellular carcinoma (HCC) patients.

Methods: Between February 2016 and December 2020, a total of 228 HCC patients (diameter $>5$ cm) who underwent HAIC alone (HAIC group, $n=135$) or HAIC and sequential ablation (HAIC-ablation group, $n=93$) treatment were reviewed. We applied the inverse probability of treatment weighting (IPTW) to adjust for potential bias of two treatment groups. The overall survival (OS) and progression-free survival (PFS) were compared with Kaplan–Meier curves. The Cox regression model was used to identify independent prognostic factors. And a prediction nomogram based on these independent prognostic factors was built, aiming to make probabilistic survival predictions and estimate personalized ablation benefits.

Results: After a median follow-up of 17.9 months, HCC patients in the HAIC-ablation group have longer significantly OS and PFS than those in the HAIC alone group (median OS: 22.2 months vs. 14.5 months; median PFS: 8.5 months vs. 4.6 months; both, $p<0.001$). The IPTW-adjusted analysis revealed similar findings (both, $p<0.001$). Tumor size, tumor number, and treatment modality were identified as independent prognostic factors for OS. The nomogram based on these factors showed favorable discrimination and well calibration.

Conclusions: HAIC and sequential ablation provided significant survival benefits in patients with large HCC. The nomogram could help predict individual survival probabilities and estimate personalized sequential ablation benefits.

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common malignancy resulting from hepatitis viral infections \cite{1,2}. It is now the second leading cause of cancer-related deaths worldwide \cite{3}. In the precision medicine era, various treatment modalities are recommended for HCC across different stages, such as surgical resection (SR), liver transplantation, thermal ablation (TA), transcatheter arterial chemoembolization (TACE), and targeted molecular therapy \cite{4}. However, HCC is a heterogeneous disease mainly due to heterogeneous hepatic functions and tumor burdens \cite{5}. Clinically, the patients with large or giant HCCs have limited treatment options and dismal prognoses \cite{6,7}. Most studies have reported that the HCC patients beyond up-to-seven criteria became refractory to repeat TACE \cite{8}. Moreover, some oncologists have suggested that SR provides significantly better survival than TACE and TA for large solitary HCC regardless of tumor stage \cite{9}. Unfortunately, most patients with large HCC lost the opportunity of SR because of diffuse distribution and colossal trauma.

The sequential treatments customized to specific patients based on the presented treatment rankings can provide superior clinical outcomes and further improve the prognosis of patients with high tumor burden \cite{7,10,11}. Keara English et al. have indicated that HCC patients who received TACE combined with sequential TA and stereotactic body radiation therapy (SBRT) can prolong survival time \cite{12}. Chuan Xu et al. suggest that sequential TACE is an effective treatment to improve resection opportunity for HCC \cite{13}. Besides, hepatic arterial infusion chemotherapy (HAIC) is also an effective and safe transcatheter chemotherapy compared with systemic chemotherapy \cite{14}. HAIC can directly inject chemical drugs into the tumor inside through the blood supply artery, with the advantages including higher local concentrations, more substantial anti-tumor efficacy, and lower systemic toxicity based on the first-pass effect. Increasing evidence demonstrates that HAIC with various regimens was superior to...
sorafenib for large HCC in the advanced stage [14–16]. Zhao Ming et al. had confirmed the effectiveness of HAIC of FOLFOX (oxaliplatin plus fluorouracil and leucovorin) regime for advanced HCC [17]. The objective response rate (ORR) and disease control rate (DCR) achieved 47.8% and 79.4%, respectively. However, the effectiveness and safety of HAIC and sequential ablation treatment (HAIC-ablation) for HCC remains unclear until now. Therefore, identifying patients who can benefit more from HAIC-LT is of great necessity.

Here, we compare the efficacy and safety of HAIC-ablation with that of HAIC alone treatment in patients with large HCC. Moreover, we also develop a nomogram model that could predict individual survival and estimate individualized sequential ablation benefit.

Materials and methods

Study population

This retrospective study obtained institutional review board approval from Ethical Review Committee of human related scientific research in the First Affiliated Hospital of Jinan University. The requirement for patient informed consent was waived due to the anonymization of individual data. This study was conducted following the principles of the Declaration of Helsinki.

Between February 2016 and December 2020, HAIC was used as an initial treatment in 1125 consecutive patients with unresectable HCC were reviewed in the databases. HCC was diagnosed based on the European Association for the Study of Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines [18,19]. The inclusion and exclusion criteria were as follows: (a) age 18–75 years; (b) patients with Eastern Cooperative Oncology Group (ECOG) performance status <2; (c) Child-Pugh class A liver function; (d) tumor size >5 cm. The exclusion criteria were as follows: (a) patients underwent other treatments before HAIC; (b) treatment history of any systemic therapy; (c) combined with other malignancies; (d) Child-Pugh class B or C liver function; (e) image data missing; (f) lost to follow-up. Among them, 498 patients with large HCC and Child-Pugh A liver function and met our inclusion and exclusion criteria. Finally, patients who underwent HAIC (n = 135) and HAIC-ablation (n = 93) for HCC were included in our study. The HCC patients enrollment pathway was illustrated in Figure 1.

HAIC procedure

HAIC procedure has been described in the previous report [17]. The catheter was inserted into the femoral artery using the Seldinger technique and advanced into the celiac artery. A micro-catheter was inserted and located in the feeding hepatic artery. All procedures were performed using digital subtraction angiography (Philips, type FD 20 1250 mA, Amsterdam, the Netherlands). The artery sheath catheter was inserted into the femoral artery using the modified Seldinger technique. A 5-Fr Yashiyo catheter (Terumo, Tokyo, Japan) was advanced into the celiac trunk and superior mesenteric artery to assess the feeding hepatic artery. 2.7-Fr micro-catheter (Terumo, Tokyo, Japan) was inserted in the feeding artery. The chemo-drugs were given by hepatic arterial infusion through the micro-catheter. A modified FOLFOX6 regimen, including oxaliplatin (130 mg/m² infusion for 3 h on day 1), leucovorin (200 mg/m² for 3–5 h on day 1) and Fluorouracil (400 mg/m² in bolus, and then 2,400 mg/m² continuous infusion 46 h) was applied. Treatment was repeated every 21 days and commonly 4–6 cycles unless intrahepatic lesions progressed or toxicity became unacceptable.

Follow-up protocol

Patients were censored at the last follow-up date (January 31, 2021). Routine contrast-enhanced images including CT or MRI, serum tumor, and hepatic function markers...
(α-fetoprotein, AFP; albumin and total bilirubin, and so on) were obtained within one week before and after treatment. And these examinations were assessed at 1–3 months after HAIC therapy, with every six months follow-up after that. If we found suspecting metastasis, chest CT, whole-body bone scans, or positron emission tomography (PET)-CT were performed selectively.

Clinical outcomes

We compared the survival outcomes between the HAIC group and HAIC-ablation group. The primary endpoints were overall survival (OS) and progression-free survival (PFS) in this study. The second endpoint was CR rate (CRR). The third endpoint was the ALBI score changes and AFP level from the first HAIC treatment to the end of treatment. OS was calculated from the initial treatment date to the death date of any cause or last follow-up date. PFS was measured from initial treatment until tumor progression, death, or deadline for follow-up, respectively. Treatment response (TR) of HAIC was assessed by dynamic CT or MRI based on modified Response Evaluation Criteria in Solid Tumor (mRECIST), including complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD), which was performed every 4–6 weeks. All images were reviewed and evaluated independently by two senior radiologists who were blinded to clinical procedures at the time of data collection to confirm agreement on TR. ALBI score was calculated before treatment using the appropriate clinical parameters were defined as follows: (log 10 bilirubin[BI] [µmol/L] × 0.66 + (albumin[AL] [g/L] × −0.085)), (grade 1, 2, and 3 ≤−2.60, −2.60 to −1.39, and >−1.39, respectively) [20]. The infusion-related reaction (IRR) was defined as reactions during the HAIC procedure and the FOLFOX regime. Major complication-related reaction (IRR) was defined as reactions during the HAIC procedure and the FOLFOX regime. The continuous variables were analyzed using the two samples t-test if the normality assumption was satisfied; otherwise, the Wilcoxon rank-sum test was used. Categorical variables were analyzed using the χ² test. Inter-observer consistency on treatment response evaluation was analyzed using Cohen’s kappa statistics. The OS and PFS were estimated separately to confirm tumor response, yielding a final kappa value of 0.84 (95% CI: 0.76–0.94). There were 74 (54.8%) progression events in the HAIC group, and 25 (18.5%) events were extrahepatic metastasis (10 in the lung, 12 in the lymph node, and three both in the lung and lymph node). In the HAIC-LT group, 55 (59.1%) progression events were observed, and 19 (20.4%) were extrahepatic metastasis (10 in the lung, 1 in the adrenal gland, five in the lymph node, and three both in lung and in lymph node). The baseline characteristics of 228 patients who underwent HAIC alone or HAIC-ablation are outlined in Table 1. Significant differences were observed in age, ascites, ALBI grade, tumor number, extrahepatic metastasis, and BCLC grade.

Comparison of clinical outcomes between different treatment modalities

In the unadjusted Kaplan–Meier analyses, the estimated 1-, 2-, and 3-year OS and PFS rates in the HAIC group were significantly lower than the HAIC-LT group (OS: 64.3% vs. 91.1%, 27.7% vs. 74.3%, 16.0% vs. 64.1%; PFS: 32.0% vs. 61.2%, 16.1% vs. 34.4%, 12.1% vs. 29.5%; both p-values <0.001; Figure 2(A,B)). Following the IPTW procedure, patient characteristics between the two groups were well balanced, with almost all absolute standardized mean differences reducing to less than 0.1. IPTW-adjusted Kaplan–Meier analyses revealed similar OS and PFS results (both of IPTW-adjusted p-values <0.001; Figure 2(C,D)). Six-month conditional landmark analyses also revealed similar findings (Figure 2(E,F)).

Change of hepatic function and AFP level

The ALBI score and AFP level were measured from baseline to post-treatment initiation. The change of ALBI score from baseline to the end of treatment was −2.61 to −2.32 in the HAIC group (p = 0.258) and −2.72 to −2.52 in the HAIC-ablation group, respectively. The ALBI score worsened significantly in HAIC group (+0.22 [−0.05 to +0.73], p < 0.001) and HAIC-ablation group (+0.22 [−0.07 to +0.69], p = 0.002) (Figure 3). The ALBI score showed no significant deterioration

Results

Patient characteristics

The median follow-up duration was 17.9 months (IQR, 6.4–41.2 months). We observed 81 (60.0%) death events in the HAIC alone group and 23 (24.7%) in the HAIC-ablation group. Two radiologists examined all the post-HAIC images independently to confirm agreement on TR. ALBI score was calculated before treatment using the appropriate clinical parameters were defined as follows: (log 10 bilirubin[BI] [µmol/L] × 0.66 + (albumin[AL] [g/L] × −0.085)), (grade 1, 2, and 3 ≤−2.60, −2.60 to −1.39, and >−1.39, respectively) [20]. The infusion-related reaction (IRR) was defined as reactions during the HAIC procedure and the FOLFOX regime. Major complication-related reaction (IRR) was defined as reactions during the HAIC procedure and the FOLFOX regime. The continuous variables were analyzed using the two samples t-test if the normality assumption was satisfied; otherwise, the Wilcoxon rank-sum test was used. Categorical variables were analyzed using the χ² test. Inter-observer consistency on treatment response evaluation was analyzed using Cohen’s kappa statistics. The OS and PFS were estimated separately to confirm tumor response, yielding a final kappa value of 0.84 (95% CI: 0.76–0.94). There were 74 (54.8%) progression events in the HAIC group, and 25 (18.5%) events were extrahepatic metastasis (10 in the lung, 12 in the lymph node, and three both in the lung and lymph node). In the HAIC-LT group, 55 (59.1%) progression events were observed, and 19 (20.4%) were extrahepatic metastasis (10 in the lung, 1 in the adrenal gland, five in the lymph node, and three both in lung and in lymph node). The baseline characteristics of 228 patients who underwent HAIC alone or HAIC-ablation are outlined in Table 1. Significant differences were observed in age, ascites, ALBI grade, tumor number, extrahepatic metastasis, and BCLC grade.

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between the two groups, but the AFP level showed significant deterioration in the HAIC-ablation group \((+11528 \text{ ng/ml} - 5.62 \text{ to } +121000 \text{ ng/ml}), p < 0.001\).

**Development of an individualized prediction nomogram**

The results of univariate Cox regression analyses for OS were summarized in Table 2. The variables with a \(P\)-value less than 0.1 were further considered in the stepwise multivariate modeling. The final multivariate Cox regression model identified three independent prognostic factors for OS, including tumor size (HR: 95%), tumor number, and treatment modality (Table 2). The three independent prognostic factors were applied to construct a prediction model. The prediction model was visualized via an easy-to-use nomogram (Figure 4(A)), exhibiting favorable discrimination (tAUC at 3-year: 0.788, Figure 4(B)) and well calibration (Figure 4(C)).

**Complications and adverse events**

No death in the two groups was directly related to HAIC. The complications and AEs were shown in Table 3. In the HAIC group, a median of four HAIC cycles (range, 2–9) was performed during the study, and two major complications (1.5%; two of 135 patients) occurred, including thrombocytopenia and massive ascites. The grades 1–2 and 3–4 of AEs were found in 116 of all 135 patients (85.9%) and six of all 135 patients (4.4%). Among them, IRR was observed in 11 of all 135 patients (8.1%), including six (3.3%) with mild to moderate vomiting, two (1.5%) with diarrhea, two (1.5%) with...
anorexia, four (3.1%) with constipation, three (2.3%) with mild abdominal pain, and two (1.5%) with severe vomiting. Dose reduction was performed in two (1.5%) patients because of grade 4 leukopenia and neutropenia, respectively. In the HAIC-LT group, a median of four HAIC cycles (range, 1–8) was performed during the study. And three major complications (3.2%; three of 93 patients) occurred, including anemia, biloma, and massive ascites. The grades 1–2 and 3–4

Figure 2. Kaplan–Meier curves comparison of between HAIC alone and HAIC-ablation group. A, unadjusted Kaplan–Meier curves of overall survival (OS) stratified by treatment modality. B, unadjusted Kaplan–Meier curves of progression-free survival (PFS) stratified by treatment modality. C, the inverse probability of treatment weighting (IPTW)-adjusted Kaplan–Meier curves of OS stratified by treatment modality. D, the IPTW-adjusted Kaplan–Meier curves of PFS stratified by treatment modality. E, six-month conditional landmark IPTW-adjusted Kaplan–Meier curves of OS stratified by treatment modality. F, six-month conditional landmark IPTW-adjusted Kaplan–Meier curves of PFS stratified by treatment modality.

Figure 3. The change of ALBI score from baseline to the end of treatment in HAIC alone and HAIC-ablation group.
of AEs were found in 77 of all 93 patients (82.5%) and eight of all 93 patients (8.6%). Among them, IRR was observed in seven of all 93 patients (7.5%) in the HAIC group, three (3.2%) with mild-to-moderate vomiting, one (1.1%) with diarrhea, one (1.1%) with anorexia, four (3.1%) with constipation, and one (1.1%) with right shoulder back pain. None gave up HAIC treatment due to severe hepatic function deterioration or drug-related toxicity. There were no significant differences in major complications, 1–2 and 3–4 AEs between the two treatment groups \( p = 0.195, 0.519, \) and 0.199).

**Discussion**

The current study has several significant findings that might shed light in clinical practice: i) HAIC and sequential ablation has longer OS, and PFS compared with HAIC alone in patients with large HCC; ii) the proposed prediction model based on the HAIC treatment modality, tumor size, and the tumor number could help predict individual survival and estimate personalized sequential ablation benefit.

To the best of our knowledge, this is the first study comparing sequential HAIC and sequential ablation versus HAIC alone as initial therapy for HCC. Previous studies have demonstrated that HAIC can dramatically improve survival outcomes of patients with advanced HCC due to the substantial reduction of the intrahepatic tumor burden, even in those with portal vein tumor thrombus (PVTT) or metastasis [17,23]. In the present study, 45.8% of patients have achieved OR after HAIC, which is similar to the study findings mentioned above (48.7%) even in the different BCLC staging [15]. We found that HAIC-ablation can significantly improve the clinical outcomes compared with HAIC alone, either unadjusted or adjusted for various confounding factors.

Meanwhile, a mild and acceptable risk of AEs result from HAIC procedure and related chemistry medicine can be accepted. However, tenacious continued HAIC procedures and HAIC and sequential ablation both worsen hepatic function or drug-related toxicity. There were no significant differences in major complications, 1–2 and 3–4 AEs between the two treatment groups \( p = 0.195, 0.519, \) and 0.199).

### Table 2. The results of univariate and multivariate Cox regression analyses for overall survival.

| Variable                  | Univariate Cox regression analyses | Multivariate Cox regression analyses |
|---------------------------|------------------------------------|-------------------------------------|
|                          | HR  | 95% CI | p Value | HR  | 95% CI | p Value |
| Age (year)                | 0.99 | 0.98–1.01 | 0.416 | –    | –      | –      |
| Sex                       |      |        |        | 0.740 | –      | –      |
| Female                    | Reference |        |        | –    | –      | –      |
| Male                      | 1.09 | 0.66–1.79 | 0.137 | –    | –      | –      |
| Comorbidity               |      |        |        | 0.62 | 0.33–1.17 | 0.031 |
| Absent                    | Reference |        |        | –    | –      | –      |
| Present                   | 0.72 | 0.25–0.94 | 0.242 | –    | –      | –      |
| HBC                       |      |        |        | 0.49 | 0.41–1.26 | 0.009 |
| No                        | Reference |        |        | –    | –      | –      |
| Yes                       | 0.49 | 0.41–1.26 | 0.192 | 0.49 | 0.02–0.75 | 0.003 |
| Cirrhosis                 |      |        |        | 1.92 | 1.18–3.13 | 0.001 |
| No                        | Reference |        |        | –    | –      | –      |
| Yes                       | 0.72 | 0.34–0.82 | 0.019 | 0.72 | 0.34–0.82 | 0.992 |
| ALBI                      |      |        |        | 0.53 | 0.53–1.33 | 0.004 |
| Child-Pugh score           |      |        |        | 0.53 | 0.34–0.82 | 0.002 |
| >5                        | Reference |        |        | –    | –      | –      |
| 5                         | 0.49 | 0.32–0.75 | 0.052 | 0.49 | 0.32–0.75 | 0.003 |
| Tumor size(cm) (mm)       |      |        |        | 0.53 | 0.34–0.82 | 0.052 |
| >7                        | Reference |        |        | –    | –      | –      |
| Tumor number              |      |        |        | 0.53 | 0.34–0.82 | 0.052 |
| Multiple                  | Reference |        |        | –    | –      | –      |
| Single                    | 0.53 | 0.53–1.33 | 0.111 | 0.53 | 0.53–1.33 | 0.002 |
| Extrahepatic metastasis   |      |        |        | 0.53 | 0.53–1.33 | 0.111 |
| No                        | Reference |        |        | –    | –      | –      |
| Yes                       | 1.48 | 1.00–2.21 | 0.048 | 1.48 | 1.00–2.21 | 0.048 |
| PVTT                      |      |        |        | 0.53 | 0.53–1.33 | 0.052 |
| No                        | Reference |        |        | –    | –      | –      |
| Yes                       | 1.38 | 0.93–2.01 | 0.048 | 1.38 | 0.93–2.01 | 0.048 |
| AFP level (U/L)           |      |        |        | 0.53 | 0.53–1.33 | 0.052 |
| >400                      | Reference |        |        | –    | –      | –      |
| <400                      | 0.67 | 0.45–1.00 | 0.048 | 0.67 | 0.45–1.00 | 0.048 |
| Treatment modalities      |      |        |        | 0.53 | 0.53–1.33 | 0.052 |
| HAIC                      | Reference |        |        | –    | –      | –      |
| HAIC-ablation             | 2.58 | 1.45–4.21 | 0.001 | 2.58 | 1.45–4.21 | 0.001 |
| HAI: hepatic arterial infusion chemotherapy; ECOG: Eastern Cooperative Oncology Group; INR: International Normalized Ratio; PVTT: portal vein tumor thrombus; BCLC: Barcelona clinic liver cancer; AFP: α-fetoprotein.
combined with fluorouracil, but cisplatin has inevitable toxicities, which caused more AEs after HAIC and forced physicians to reduce the dose \([25-27]\). Although this high-dose regimen can improve the therapeutic effect, it still cannot be used continuously. FOLFOX using oxaliplatin instead of cisplatin is a classic combined anti-cancer method and was proved to be effective systemically for advanced HCC. Moreover, the well-received advantage of HAIC lies in the lower incidence of AEs and major complications than systemic chemotherapy and TKIs. The incidence of grade 3–4 AEs (4.4%) and major complications (1.4%) were found in the HAIC group, and more ascites in grade 3–4 AEs were found in the HAIC-LT group, but there were no significant differences between the two groups \((p = 0.199)\) in our study. These results confirm further that HAIC is a safe and effective therapeutic approach for large HCC.

In this study, the target population is patients with large HCC. Therefore, minimizing the tumor burden is a crucial way to improve survival. The median OS in the HAIC-ablation group reached 22.2 months, which is higher significantly than that in the HAIC alone group \((p < 0.001)\) and superior to that of those patients who received sorafenib in previous study (6.2 months of median OS) \([14,28,29]\). In the past decade, the therapeutic effect of HAIC on HCC is increasingly recognized by physicians. However, there is currently no consensus regarding whether HCC patients with high tumor burden should receive ablation after HAIC or not. Therefore, identifying HCC patients who might benefit more from HAIC-ablation plays a vital role in therapeutic decision-making toward precision oncology. Clinically, prediction models based on patient characteristics have been widely used to stratify patients and estimate stratified treatment effects.

Figure 4. A, the prediction model visualized via a nomogram, which can easily predict 1-, 2-, and 3-year overall survival. B, the discrimination of prediction model was assessed using the time-dependent area under the receiver operating characteristic curve. C, the calibration of prediction model was evaluated using calibration plot.
More accurate estimation of treatment effect can identify suitable patient candidates for sequential ablation, therefore avoid potentially futile local aggressive therapy. In this study, baseline clinical characteristics, including tumor size and the tumor number, were significantly associated with survival outcomes. Interestingly, for patients with a single tumor, the LT benefit was increased with tumor size, while it decreased with tumor size for patients with multiple tumors. Nevertheless, a considerable survival benefit of sequential ablation was observed universally, regardless of tumor burdens. Our findings indicated that sequential ablation should be applied routinely after HAIC treatment if patients were without known contraindications.

There are some limitations to our study. First, the risk of selection bias is unavoidable in observational studies. However, this risk has been minimized by including all HCC consecutive patients for HAIC and applying IPTW method. Second, the study cohort is a single-center, retrospective study, and the sample size is relatively small. The large-scale multicenter prospective studies are necessary to design in the future to verify our findings. Finally, to reduce selective bias, all patients with OR were enrolled; therefore, the median survival time of patients who received HAIC must be longer than that in reality. The following study needs to summarize and analyze the survival time of all patients regardless TR.

In conclusion, HAIC and sequential ablation is a safe and effective treatment in patients large HCC, significantly improving survival outcomes. We proposed nomogram could help predict individual survival probabilities and estimate personalized sequential ablation benefits.

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Table 3. Major complications and adverse events between HAIC group and HAIC-ablation group.

| Major complications and AEs | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 |
|----------------------------|-----------|-----------|-----------|-----------|
|                            | n (%)     | n (%)     | n (%)     | n (%)     |
| **Major complications**    |           |           |           |           |
| Massive ascites            | 1 (0.7)   | 2 (2.2)   |           |           |
| Thrombocytopenia           | 1 (0.7)   |           | 1 (1.1)   |           |
| Anemia                     |           | 1 (1.1)   |           |           |
| Biloma                     |           |           | 1 (1.1)   |           |
| **AEs in total**           | 116 (85.9)| 6 (4.4)   | 77 (82.5) | 8 (8.6)   |
| **Blood/bone marrow suppression** |           |           | 0.519     | 0.199     |
| Leukopenia                 | 8 (5.9)   | 1 (0.8)   | 3 (3.2)   | NA        |
| Neutropenia                | 6 (4.4)   | 1 (0.8)   | 4 (4.3)   | NA        |
| Reduced hemoglobin         | 2 (1.5)   | NA        | 1 (1.1)   | NA        |
| Coagulation disorder       | 2 (1.5)   | NA        | 1 (1.1)   | NA        |
| Elevated INR               | 7 (5.2)   | NA        | 3 (3.2)   | 1 (1.1)   |
| **Constitutional symptom** |           |           |           |           |
| Weight loss                | 56 (41.5) | NA        | 14 (15.1) | NA        |
| Fever                      | 37 (27.4) | NA        | 11 (11.8) | NA        |
| Fatigue                    | 43 (31.9) | NA        | 10 (10.8) | NA        |
| **GI disorder**            |           |           |           |           |
| Ascites                    | 11 (8.1)  | NA        | 21 (22.6) | 5 (5.6)   |
| Diarrhea                   | 2 (1.5)   | NA        | 1 (1.1)   | NA        |
| Anorexia                   | 2 (1.5)   | NA        | 1 (1.1)   | NA        |
| Constipation               | 4 (3.1)   | NA        | NA        | NA        |
| Vomiting                   | 6 (4.4)   | 2 (1.5)   | 3 (3.2)   | NA        |
| **Pain**                   |           |           |           |           |
| Abdominal nonspecific      | 3 (2.3)   | NA        | NA        | NA        |
| Right shoulder back        | NA        | NA        | 1(1.1)    | NA        |
| **Laboratory abnormalities**|           |           |           |           |
| Elevated ALT               | 76 (56.6) | 2 (1.5)   | 45 (48.4) | 1 (1.1)   |
| Elevated AST               | 69 (51.1) | NA        | 42 (45.2) | NA        |
| Elevated TBIL              | 52 (38.5) | NA        | 32 (34.4) | 1 (1.1)   |
| Elevated creatinine        | 39 (28.9) | NA        | 21 (23.0) | NA        |
| Anemia                     | 2 (1.5)   | NA        | NA        | NA        |
| Others                     | 10 (7.4)  | NA        | 5 (5.4)   | NA        |

Data in bracket was percent of patients. The data in two groups were compared by using the Chi square test. *Data were compared by using Fisher’s exact test.

TACE: transarterial chemoembolization; HAIC: hepatic arterial infusion chemotherapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; INR, international normalized ratio; TBIL, total bilirubin.
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