Houseni *et al. Egyptian Liver Journal* (2023) 13:41
https://doi.org/10.1186/s43066-023-00276-6

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE

Open Access

Hepatic artery infusion chemotherapy for advanced hepatocellular carcinoma

Mohamed Houseni[1], Mahmoud Abdel Aziz Abdel Hady[1] and Sameh Abokoura[1*]

Abstract

Objective: This study's purpose was to evaluate the response, safety and overall survival of trans-arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma with preserved hepatic function.

Methods: This study was carried out on 25 patients, diagnosed with hepatocellular carcinoma (HCC) combined with portal vein tumor thrombosis (PVTT) and underwent hepatic artery infusion chemotherapy (HAIC). Radiological investigations as Triphasic CT or dynamic MRI liver assessment pre and post therapy were acquired. Intra-Arterial chemotherapeutic agent infusion using only doxorubicin was performed.

Results: Neither of the patients who underwent HAIC developed complete or partial response. Only one patient (4.8%) from 21 patients under HAIC had stable disease. 20 patients (95%) had progressive disease. Progressive disease was in form of progression at the primary tumor site in form of increased focal lesion size, number or vascular invasion. Vascular invasion was seen in one patient (4.8%) in the form of hepatic vein thrombosis. Mean progression free survival was about 2.24 ± 0.88 months. Mean overall survival was about 5.72 ± 0.89 months.

Conclusion: Our study demonstrated lower clinical efficacy and lower disease control rate of repeated HAIC using doxorubicin only infusion in case of advanced HCC with PVT as compared to combined doxorubicin and cisplatin in previous studies as well as the standard therapy with sorafenib.

Keywords Hepatic artery infusion chemotherapy, Portal vein tumor thrombosis, Advanced hepatocellular carcinoma

Background

One of the most common malignant neoplasms in humans is hepatocellular carcinoma (HCC). The development of HCC is thought to be significantly related to chronic hepatitis B virus or hepatitis C virus infection, ingesting food contaminated with aflatoxin B1, and alcohol use [1].

The portal vein is susceptible to being invaded by the tumour, leading to portal vein tumour thrombosis (PVTT) [2]. The most typical HCC presentation related to locally advanced HCC is PVTT. According to estimates, 10 to 40% of patients with HCC have PVTT at the time of diagnosis; as a result, their prognosis is incredibly poor [3].

As a palliative treatment for HCC, trans-arterial chemoembolization (TACE) has been widely used [4]. Due to the possibility that embolization could worsen liver function and cause a hepatic infarction, PVT has been classified as a relative contraindication to TACE [5].

Regardless of the extension of the tumour thrombus, HCC patients with macrovascular portal vein invasion are categorised as being in an advanced stage (stage C) under the current BCLC system. The patients are not suitable TACE candidates as a result [6].

*Correspondence:
Sameh Abokoura
samehabokoura@gmail.com
[1] Department of Radiology, National Liver Institute, Menoufia University, Shebin Elkoum, Egypt

Current treatment options include systemic therapies like chemotherapy, targeted therapy, radioembolization, and external beam irradiation for patients who are not candidates for local therapies, such as those with extrahepatic metastases and/or thrombosis in the portal vein or in its major branches [7].

Sorafenib is an oral multi-kinase inhibitor that promotes apoptosis by inhibiting tumour cell growth and angiogenesis. Raf-1 and B-Raf, the receptor tyrosine kinase of vascular endothelial growth factor receptors, and platelet-derived growth factor receptor are the targets of sorafenib. The only effective systemic therapy for patients with advanced HCC that is well tolerated is sorafenib [8].

The goal of HAIC is to minimise systemic toxicities while increasing drug concentrations in the target tumour and the liver [9].

This study's objective was to assess the response, safety and overall survival of trans-arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma with preserved hepatic function.

Methods

Our study was carried out on 25 patients, who attended the multidisciplinary HCC clinic at national liver institute, presented with HCC associated with PVTT and underwent HAIC. A written agreement was taken from all the patients under the study. In this the study a total of 25 patients were classified into Barcelona Clinic Liver Cancer (BCLC) stage C (advanced hepatocellular carcinoma) because of portal vein invasion.

We depended on the American Association for the Study of Liver Diseases (AASLD) 2018.published practice guidelines for the management of HCC.

The Inclusion criteria:

1) Patients with class A Child–Pugh.
2) No associated serious medical illness.
3) Age ≥ 18 years.
4) Performance status 0–1 for the Eastern Cooperative Oncology Group (ECOG).
5) Optimal organ and bone marrow function with total leucocytic count ≥ 3,000/mm3, platelets ≥ 100,000/mm3, aspartate aminotransferase (AST), and/or alanine aminotransferase (ALT) ≤ 5 times the upper limit of normal (ULN), bilirubin ≤ 2 mg/dL, and creatinine ≤ 1.5times.ULN.

The exclusion criteria:

1) Decompensated patients (child B & C).
2) History of hepatic encephalopathy.
3) Associated co-morbidities.
4) Patients with tumors associated with arteriovenous shunt.

Full history taking, clinical examination, Laboratory investigations such as CBC, Total and direct bilirubin, serum albumin, PT-INR and Alpha fetoprotein, Echocardiography before beginning of treatment and Radiological investigations as Triphasic CT or dynamic MRI liver assessment pre and post therapy were done.

Intra-arterial chemotherapy procedures

The inguinal area was punctured to reach the right femoral artery through seldinger technique, followed by introduction of a guide wire followed by a catheter to reach the celiac trunk, followed by passage of the catheter to the proper hepatic artery. After determination of the major feeding artery of tumor, chemotherapeutic agents were infused by the usage of an automatic infusion pump. After the procedure was completed, the catheter and the sheath are removed. The same technique will be repeated in each therapy of the intra-arterial chemotherapy.

Chemotherapy regimens

The dose of the Doxorubicin was about 50 mg/m2. About 100 mL normal saline was used for the dilution of the chemotherapy, and will be infused over 10 min. Premedication included dexamethasone, antiemetic, antihistaminic as well as proton pump and adequate hydration.

Response evaluation

We depend upon the CT scans or MRI scans done before and after every two sessions of treatment, and the modified RECIST criteria were used to assess the effect of the therapy:

Complete response (CR): Absence of any tumoral enhancement.
Partial response (PR): Decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions by at least a 30%, taking the baseline sum of the target lesion's diameters as a reference.
Stable disease (SD): Neither partial response nor progressive disease.
Progressive disease (PD): The total diameters of viable (enhancing) target lesions increased at least by about 20%, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

We will repeat the technique after 4–6 week intervals, can be repeated for 6 cycles and we will stop it when

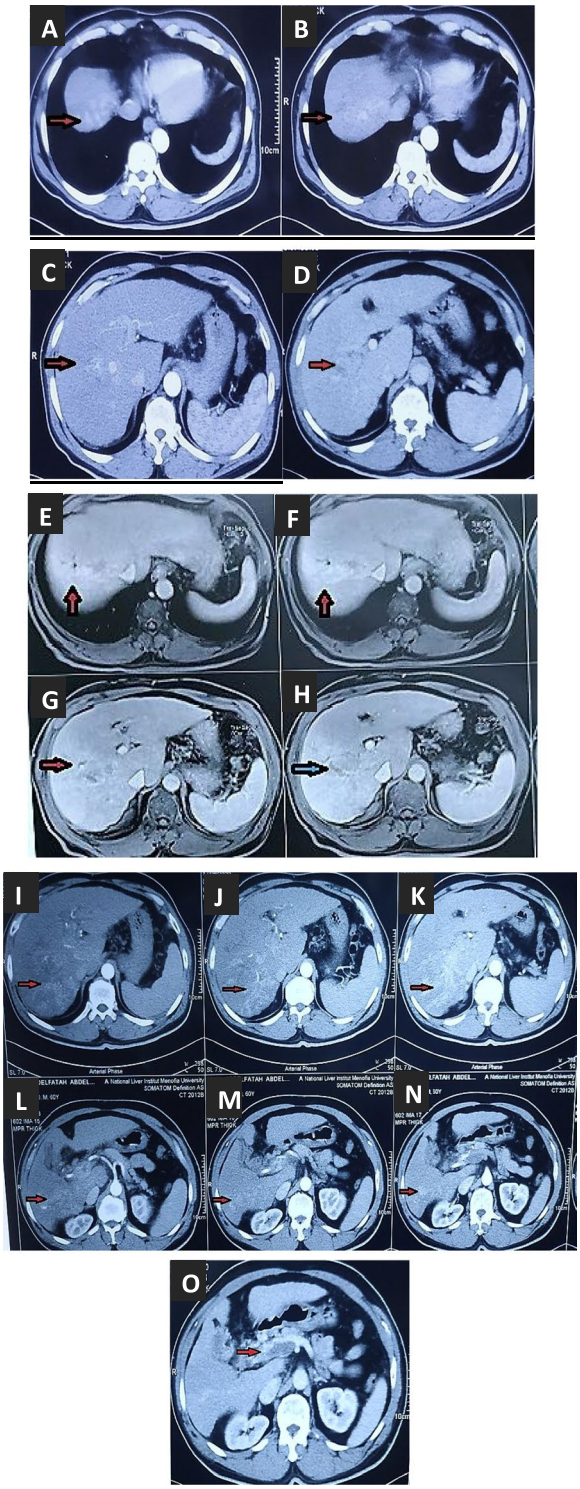

Fig. 1 57 years old male patient with cirrhotic liver and HCC. Triphasic CT before start of HAIC (A to D images): **A** & **B**, images show right lobe segment VII & VIII HCC. **C** & **D**, images show malignant thrombosis of the right portal branch. Dynamic MRI at the 1st follow up after HAIC (**E**-**H** images): show stationary course of right lobe HCC (Red arrow) and right portal vein thrombosis (Blue arrow). Triphasic CT at the 2nd follow up after HAIC (I to O images): **I**-**N** images show increased size of the lesion to involve segments V & VI of the liver. **O** image revealed propagation of the right portal vein thrombus to main portal vein

disease progression, impaired liver function, severe side effects, or intolerance and the EF decreased below 50% occur.

Statistical methods

Statistical package of social sciences (SPSS 22.0, IBM/SPSS Inc., Chicago, IL) was used for analyzing the results.

The quantitative data was summarized as mean (X), standard deviation (SD), median, and interquartile range (IQR) and for qualitative data we used frequency with percentage (%). The expression of the normally distributed data as mean ± SD while those that are not normally distributed was expressed as median and range or IQR.

Results

Our study was conducted on 30 patients underwent HAIC. Five patients received single session of intra-arterial chemotherapy and dropped due to COVID 19 outbreak.

The remaining 25 patients (21 males and 4 females) with the age showing mean value of 52.00 ± 6.08 and age ranging between 43 – 66, were enrolled in our study. Three patients died after two cycles from the beginning of HAIC. Another patient developed marked deterioration of the liver function after the second session of HAIC.

The whole 25 patients (100%) under HAIC were classified as class A according to child–Pugh classification.

In our study 5 patients had left portal vein thrombosis and 19 patients had right portal vein thrombosis as detected by pretherapy triphasic CT. Only one patient had total portal vein thrombosis (right, left and main portal).

Five patients had multiple hepatic focal lesions while the remaining 20 patients had a single focal lesion. The sizes of the focal lesions were equal to or more than 5 cm in 23 patients (92%), and less than 5 cm in 2 patients (8%).

Follow up by triphasic CT revealed increased size of focal lesions in 20 patients (95%) from 21 patients (Figs. 1 and 2), increased number of focal lesions in 5 patients

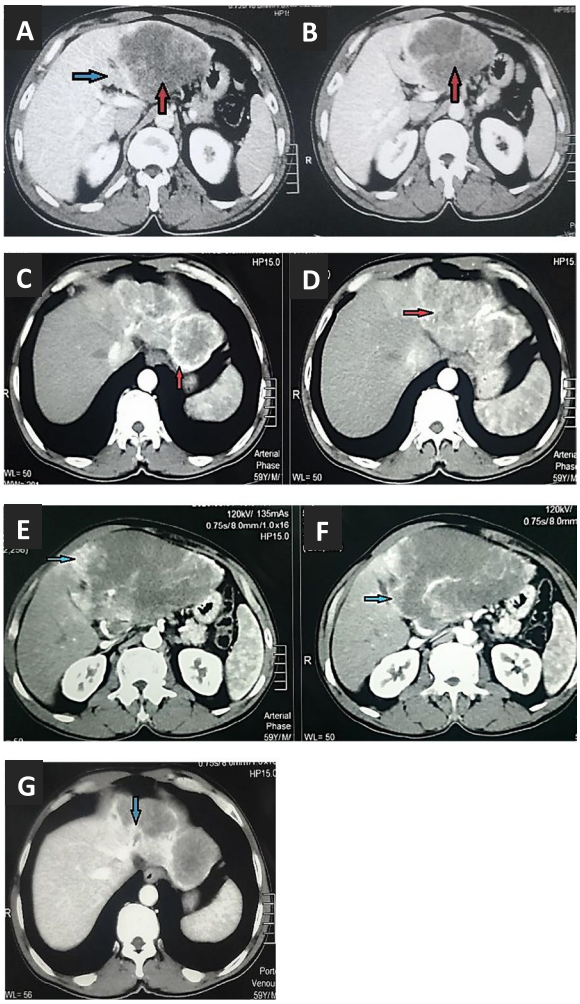

Fig. 2 47 years old male patient with cirrhotic liver and HCC. Triphasic CT before start of HAIC (**A** & **B** images): show left lobe segment II& III HCC (red arrow) with left portal vein thrombosis (blue arrow). Triphasic CT at the 1st follow up after HAIC (**C**-**G** images):**C**-**F** images show increased size of the previously noted HCC that extends to involve segment IV. **G** image shows newly developed left hepatic vein thrombosis

(23.8%) from 21 patients, progression of portal vein thrombus in 6 patients (28.57%) from 21 patients.

Four patients (19%) developed ascites after the 1st 2 cycles from 21 patients under HAIC. Only three patients (14.3%) developed complications in form of hyperbilirubinemia, one of these patients complicated after 6 cycles and the other two patients complicated after 1st 2 cycles. Three patients (12%) from 25 patients died after 1st two cycles of HAIC.

Neither of the patients who underwent HAIC developed complete or partial response. One patient (4.8%) from 21 patients under HAIC had stable disease. 20 patients (95%) from 21 patients had progressive disease. Progressive disease was in form of progression at the primary tumor site in form of increased focal lesion size, number or vascular invasion. Vascular extension was seen in one patient from 21 patients under HAIC in the form of hepatic vein thrombosis. Treatment efficacy at 6 months in patients under HAIC was summarized in (Table 1) (Fig. 3).

Table 1 Treatment efficacy at 6 months in patients under HAIC

Parameter	GI IACT ($n=21$)
Efficacy at 6 months [n (%)]	
Complete response (CR)	0 (0.0%)
Partial response (PR)	0 (0.0%)
Stable disease (SD)	1 (4.8%)
Progressive disease (PD)	20 (95.2%)
Response rate	0 (0.0%)
Disease control rate	1 (5.6%)
Progression-free survival (months)	
Mean ± SD	2.24 ± 0.88
Median	2.00
Range (min–max)	2.00—6.00
Overall survival (months)	
Mean ± SD	5.72 ± 0.89
Median	6.00
Range (min–max)	2.00—6.00

Mean progression free survival was about 2.24 ± 0.88 months. Mean overall survival was about 5.72 ± 0.89 months (Table 1) (Fig. 4).

Discussion

One of the common causes of neoplastic-related mortality globally is the hepatocellular carcinoma. Patients with liver cirrhosis associated with early HCC could be treated by surgical or local ablative procedure with the possibility of a long-term survival [8]. For patients with extrahepatic spread and/or portal vein extension will be under, systemic chemotherapy or infusion chemotherapy through the hepatic artery [9].

HAIC differs from the systemic therapy in being an intra-arterial procedure resulting in increased local concentration of a drug improving the effect of therapy, while the systemic exposure to the chemotherapy remains low.

Our study was conducted on 25 patients (21 males and 4 females). Their ages ranged between 43–66 years with mean age of 52 years. This study is compared to similar studies as Ma Ming-chun et al. [9] that included 50 patients (48 males and 2 females) with ages ranged between 39–75 years with mean age of 52 years were under HAIC by Doxorubicin and cisplatin. Another similar study done is Jeong SW et al. [8] in which 20

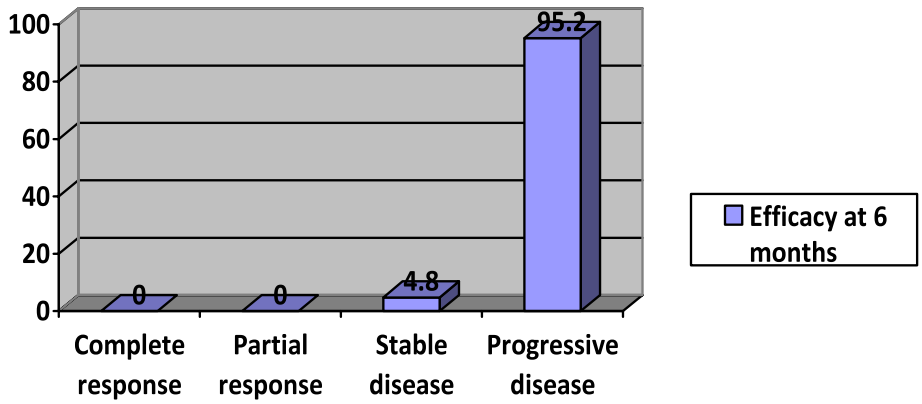

Fig. 3 Treatment efficacy at 6 months in patients under HAIC

patients (11 males and 9 females) were under sorafenib with ages ranged between 49–75 years with mean age of 59 years and 21 patients (all was males) with age ranged between 33–75 years with mean age 51 years under HAIC by cisplatin and 5-fluorouracil (5 –FU).

In our study, we compared trans-arterial doxorubicin infusions with shorter infusion times to protracted infusions of low-dose cisplatin and 5-FU, which required a relatively long-term treatment and hospitalization, as well as a permanent injection port implantation at the femoral site. Ma Ming-chun et al. [9], which used Doxorubcin and cisplatin and also Jeong SW et al. [8] which used 5-FU and cisplatin were used and by the injection port infusion.

In our study, none of the patients under HAIC showed complete or partial response (0%) while 1 patient (4.8%) showed stable disease for 6 months and 20 patients (95%) showed progressive disease for 6 months, this is in comparison to Jeong SW et al. [8] which showed no complete response in the study (0%) while partial response achieved at 4 patients (19%) while 5 patients (23.8%) achieved stable course of the disease and 12 patients (57.1%) showed progressive course of the disease in the patient under HAIC. Compared to sorafenib as stated by Jeong SW et al. [8], two patients (10%) showed partial response, 5 patients (25%) showed stable disease and 13 patients (65%) showed progressive disease. And compared to Ma Ming-chun et al. [9] which stated that none of the patients under HAIC showed complete response, 11 patients (22%) showed partial response, 11 patients (22%) showed stale disease, 18 patients (36%) shows progressive disease.

In our study the median overall survival was 6 months compared to 7.3 months in the HAIC group and 4.9 months in the sorafenib group according to Jeong SW et al. [8] while it was 12 months in patients under HAIC according to Ma Ming-chun et al. [9].

The median progression free survival was 2 months in our patients under HAIC, compared to 3months for IACT group and 2 months for sorafenib group according to Jeong SW et al. [8] and 3.6 months in the IACT group according to Ma Ming-chun et al. [9].

The percentage of patients with the best response rating of a complete response, a partial response, or stable disease—according to modified RECIST, which was maintained for at least 28 days after the initial demonstration of that rating based on an independent radiological review, was considered the disease control rate. In our study the DCR was 1 (5.6%) patient, compared to 8 (38.1%) in the HAIC group and 7(35%) in the sorafenib group according to Jeong SW et al. [8] and 70% in the HAIC as mentioned at Ma Ming-chun et al. [9]

Disease progression at the primary tumor site including increased lesion size, number and macroscopic vascular invasion, was the major cause for discontinuation, however other causes such as development of complications and deterioration of the liver function may be other causes for disease discontinuation.

Development of ascites was associated with disease progression in 4 (19%) patients from 21 patients under HAIC. Worsening of the liver function seen in 3 (14.3%) patients from 21 patient under HAIC, compared to Ma Ming-chun et al. [9] in which worsening of the liver function seen only in one patient (3.3%) and seen also in 3 (14.3%) patients as seen in Jeong SW et al. [8].

The small sample size and potential bias caused by the small number of patients were the study's limitations.

Conclusion

Our study showed low clinical effect as well as marked side effects of repeated sessions of trans-arterial chemotherapy using doxorubicin by infusion in case of terminal stages of HCC with portal vein thrombosis as compared to combined doxorubicin and cisplatin in previous

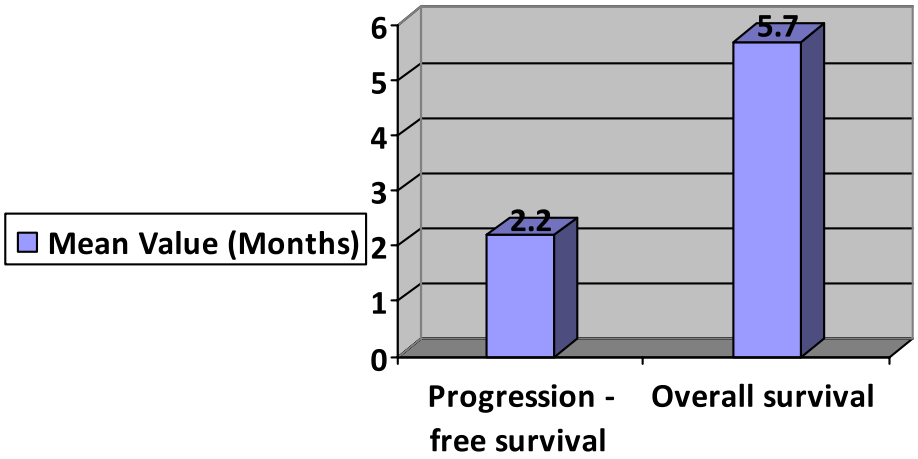

Fig. 4 Mean levels of progression-free and overall survival (months) in patients under HAIC

studies. The standard therapy with sorafenib in previous studies also was superior to the HAIC with better survival rate, efficacy as well as disease control rate.

Acknowledgements
Not applicable.

Authors' contributions
HSA: Conceptualization and Data curation: SA, Formal analysis: SA, MH, Investigation: MA, Formal analysis: SA, MA, MH, Methodology: MH, Project administration and resources: SA, MA, Software: SA, Supervision: MH, Validation and Visualization: MA, MH, writing original draft: SA, writing review, revised & editing: SA, MH, MA. "All authors read and approved the final manuscript".

Funding
This study had no funding from any resource.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional Review Board (IRB)" of National Liver Institute Menoufia University and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from the patients.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

Received: 25 January 2023 Accepted: 6 August 2023
Published online: 10 August 2023

References

1. Gong L, Li Y, SU Q, et al (2010) Clonality of Nodular Lesions in Liver Cirrhosis and Chromosomal Abnormalities in Monoclonal Nodules of Altered Hepatocytes. Histopathology 56(5):589–599
2. Zhang Z, Guo J, Zhang Z et al (2011) Therapeutic options for intermediate-advanced hepatocellular carcinoma. WJG 17(13):1685–1689
3. Quirk M, Kim Y, H, Saab S, et al (2015) Management of hepatocellular carcinoma with portal vein thrombosis. World J Gastroenterol 21(12):3462–3471
4. Bruix J, Reig M, Sherman M (2016) Evidence-Based Diagnosis, Staging, and Treatment of Patients with Hepatocellular Carcinoma. Gastroenterology 150(4):836–853
5. Silva J, Berger N, Tsai S et al (2017) Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombosis: a systematic review and meta-analysis. Review article 19(8):P659-666
6. Lurje I, Czigany Z, Bednarsch J et al (2019) Treatment Strategies for Hepatocellular Carcinoma-A Multidisciplinary Approach. Int J Med Sci 20(6):1465
7. Gholam PM, Iyer R, Johnson MS (2019) Multidisciplinary Management of Patients with Unresectable Hepatocellular Carcinoma: A Critical Appraisal of Current Evidence. Cancers (Basel) 11(6):873. https://doi.org/10.3390/cancers11060873. (Published 2019 Jun 22)
8. Jeong SW, Jang JY, Lee JE, et al (2012) The efficacy of hepatic arterial infusion chemotherapy as an alternative to sorafenib in advanced hepatocellular carcinoma. Asia Pac J Clin Oncol 8(2):164–171
9. Ma MC, Chen YY, Li SH, et al (2014) Intra-Arterial Chemotherapy with Doxorubicin and Cisplatin Is Effective for Advanced Hepatocellular Cell Carcinoma. Sci Worl J 2014:160138, 8. https://doi.org/10.1155/2014/160138

Publisher's Note