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TRANSARTERIAL CHEMOEMBOLIZATION IN HEPATOCELLULAR CARCINOMA TREATMENT DURING THE COVID-19 PANDEMIC

TRANSARTERIJSKA HEMOEMBOLIZACIJA U TRETMANU HEPATOCELULARNOG KARCINOMA TOKOM COVID-19 PANDEMIJE

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Abstract

The COVID-19 pandemic had a significant impact on the treatment of hepatocellular carcinoma as a cause of delays in diagnosing and treating patients due to the limitations in access to reference centers. The availability of human resources for the care of patients with hepatocellular carcinoma has decreased, as has the availability of hospital beds and operating rooms. On the other side morbidity and mortality related to treatment are increased in patients with cirrhosis and cancer due to their immunocompromised status and thus a higher chance of contracting a severe form of the COVID-19 disease. In order to handle such a challenging situation it became essential to revise the actual recommendations for hepatocellular carcinoma strategies during COVID-19 pandemic and adapt them to daily practice following the current legislation while respecting the principles of good clinical practice.

Keywords:
transarterial chemoembolization, hepatocellular carcinoma, COVID-19

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Sažetak

Pandemija bolesti izazvane koronavirusom 19 (COVID-19) ima značajan uticaj na lečenje hepatocelularnog karcinoma uzrokovanjem kašnjenja u dijagnostikovanju i lečenju pacijenata zbog ograničenja u pristupu referentnim centrima. Smanjena je dostupnost ljudskih resursa za negu pacijenata sa hepatocelularnim karcinomom, kao i dostupnost bolničkih kreveta i operacionih sala. S druge strane, kod pacijenata sa cirozom i karcionomom su, zbog njihovog imunokompromitovanog statusa, povećani postterapijski morbiditet i mortalitet, kao što su i veće šanse da obole od teške forme COVID-19 bolesti. U suočavanju sa tako izazovnom situacijom od suštinskog je značaja da se revidiraju aktuelne preporuke za strategije lečenja hepatocelularnog karcinoma tokom pandemije COVID-19 i da se prilagode svakodnevnoj praksi, u skladu sa važećim zakonodavstvom, uz poštovanje principa dobre kliničke prakse.

Ključne reči:
transarterijska hemoembolizacija, hepatocelularni karcinom, COVID-19

Introduction

Since a global pandemic was declared, a deep impact on hospital organizations has been made with the necessity to accommodate critically ill COVID-19 patients. Movement bans and restrictions introduced with the aim of preventing the spread of the COVID-19 infection have resulted in fewer newly diagnosed cases of patients suffering from hepatocellular carcinoma (HCC), and therefore in the delay of treatment. The screening was interrupted, treatments canceled and follow-up delayed (1), thus management of cancer patients became more complicated with the need to make a balance between delayed cancer treatment against the risk of SARS-CoV-2 virus infection. Elective operations have been postponed in order to direct healthcare workers to the treatment of patients with COVID-19 infection and to increase the capacity of the health system to receive, treat and rehabilitate patients with viral pneumonia. However, postponing the surgical treatment of cancer carries the risk of tumor progression to a stage when it is no longer resectable, thus turning a potentially curative therapeutic option into a palliative/cytoreductive one with a significantly worse therapeutic outcome.

International multidisciplinary panels discussed all available therapeutic strategies that would be rational to apply in the newly emerging circumstances of the pandemic and certain guidelines for postponing the operative treatment of HCC during the pandemic (1). Following the EASL-ESCMID guidelines, healthcare providers should strive to maintain care of patients with liver cirrhosis and to find a way to provide this group of patients with priority in treatment during the era of limited healthcare resources (2). Unfortunately, evidence-based medicine guidance for interventional radiology treatment of patients with HCC during the pandemic is not yet available (3).

A certain number of professional society guidelines (**table 1**) including recommendations for treatment strategies for patients with HCC during the COVID-19 pandemic have been published (4-8) to try to deal with the current situation. However, the true impact of the pandemic on the treatment of patients with HCC is still unknown (1).

Methods

This Rapid Review of the published literature was done with the purpose of combining international recommendations with local regulations and the possibilities of our health system to develop guidelines for the TACE treatment of patients with HCC during the COVID-19 pandemic. A literature search was performed by using PubMed-referenced publications on the management of HCC during the COVID-19 pandemic. Nonoperative treatment strategies presented in this narrative review were discussed by the multidisciplinary board at the author's institution and thus represent a consensus opinion adapted to our country's requirements.

Table 1. Professional Society Guidelines on HCC management during the COVID-19 pandemic.

Professional society	Reference
American Association for Study of Liver Disease (AASLD)	Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement (12)
European Association for Study of the Liver (EASL)	Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper (33)
Asian-Pacific Association for the Study of the Liver Society (APASL)	APASL practical recommendations for the management of hepatocellular carcinoma in the era of COVID-19 (5)
Sao Paulo Clinicas Liver Cancer Group Multidisciplinary Consensus Statement (HC-FMUSP)	Management of hepatocellular carcinoma during the COVID-19 pandemic - São Paulo Clínicas liver cancer group multidisciplinary consensus statement (28)
International Liver Cancer Association (ILCA)	Management of HCC during COVID-19: ILCA Guidance (27)

Recommendations

Patients with HCC are susceptible to the SARS-CoV-2 virus due to its proven effect on hepatic injury (9) and patient immunocompromised states (10). Providing surveillance and monitoring of hepatocellular carcinoma while minimizing the risk of exposure to COVID-19 infection must be carefully balanced (11). Priority must be given to patients in whom the expected benefit from therapy outweighs the risk of COVID-19 infection.

The pandemic is proven to induce delays in diagnosis and treatment of patients with HCC but no significant modification in treatment strategy (1). In order to avoid degrading the clinical benefit of treatment or causing more complications during the pandemic the local expertise should be optimized rather than new techniques implemented (3). A consensus has been reached that patients with hepatocellular carcinoma should receive locoregional therapy during the pandemic (12) at COVID-19-free institutions when feasible (7).

Locoregional therapies

Locoregional therapies include transarterial chemoembolization, transarterial radioembolization, and thermal ablation stereotactic body radiotherapy (SBRT). For the intermediate stage of HCC TACE is a preferred local treatment (15). In most cases, it is a single-day procedure with high effectiveness considered as a standard of care for this group of patients.

The TACE treatment could also be used to maintain advanced HCC tumor control in cases when surgical treatment is not indicated (16). Since large tumors (> 5 cm), multifocal liver lesions and vascular invasion are contraindications to surgery vascular cytoreductive interventions such as TACE or TARE are recommended (5). In case no extrahepatic spread of the malignant disease is confirmed those patients could be treated with TACE or TARE to control the disease locally and allow for evaluation of the tumor biology (17). One of the approaches in the treatment of patients with unresectable or inoperable disease is the application of TACE treatment as a palliative therapy to achieve local tumor control, preventing disease progression and improving survival. With the application of TACE therapy, patients spend most of their time at home, and hospital resources can be diverted to the treatment of other patients, which is very important in pandemic conditions.

cTACE vs DEB-TACE

In most cases, HCC is mainly vascularized from the hepatic artery which makes transarterial therapy feasible. The concept of conventional TACE (cTACE) considers catheterization of the tumor-feeding artery followed by injection of chemoembolization material (doxorubicin or cis-platin mixed with lipiodol), leading to ischemic necrosis of the tumor via cytotoxic and ischemic effects without clinically significant side effects to the surrounding liver parenchyma. Dual blood supply of the liver by the portal vein and hepatic artery makes it suitable for this type of treatment. Lipiodol is a drug-carrying and embolizing agent (18) which is proven to stay within the tumor for months and washed out from non-tumor liver tissue within 4 weeks (19).

Since the use of lipiodol reduces the concentration of chemotherapeutic agents delivered to the tumor drug-eluting beads (DEBs) have been introduced as relatively new drug-delivering agents. They have been shown to allow a higher concentration of chemotherapeutic agents within the tumor in comparison with lipiodol with the release in a sustained manner over a prolonged period of time (20, 21). On the other hand, cTACE is also called „controlled" TACE due to the usage of lipiodol which is a contrast agent with a proven advantage over DEB in fluoroscopic control during application. Finally, the selection of the appropriate TACE method for locoregional treatment of HCC in every particular case is partly dependent on local expertise and preferences.

TACE is the preferred treatment for intermediate-stage HCC according to the BCLC system, however in clinical practice indications for TACE have been extended from early to even advanced-stage HCC (24). In the light of COVID-19 pandemic, TACE could also be used as bridging therapy for liver transplantation or resection (25, 26). Due to the operative treatment limitations and the risk of infection created by the pandemic for patients with HCC, certain modifications of the standard of care to fit the current situation became mandatory, and furthermore, the professional societies guidelines have been proposed (2, 5, 12, 27, 28). According to those recommendations, TACE could be considered for local disease control if necessary to delay surgery (**table 2**). During the pandemic, TACE should be performed as an outpatient procedure whenever possible, and considered a palliative treatment to control the tumor and keep the patient at home as long as possible (3).

Table 2. Recommendations for liver vascular interventions during the pandemic.

APASL	HC-FMUSP	AASLD
Vascular interventions should be suspended in patients with comorbidities that increase the risk of COVID-19	TACE/TAE could be performed as a bridge treatment to surgery or local disease control in patients with solitary nodules larger than 3 cm	Consider TACE/TARE as a bridging therapy in case of surgery delay. Consider TACE for single or multifocal HCC

APASL: Asian-Pacific Association for the Study of the Liver Society; HC-FMUSP: Sao Paulo Clinicas Liver Cancer Group Multidisciplinary Consensus Statement; AASLD: American Association for the Study of Liver Disease.

It is advised to perform a follow-up imaging and AFP check 4 - 8 weeks after TACE and every 3 - 4 months (in case of no recurrence) to assess tumor response to therapy and determine the need for repeat treatment (29). TACE procedures are repeated if residual viable tumors are detected on a control MDCT/MRI examinations (30). Longer follow-up intervals are proven to lead to a lower overall response rate for HCC patients. In case of a follow-up interval longer than 95 days, patients might experience a worse prognosis (30). In case of delayed cross-sectional imaging due to COVID-19 reasons, AFP serum values could potentially be used as a marker of tumor response to the therapy (31). To achieve greater efficiency in the treatment of patients with methods of interventional radiology, good coordination in the work of doctors of different specialties is necessary to ensure timely post-procedural control (MDCT/MR) examinations that evaluate the response to the applied therapy and plan further treatment. The evaluation of the therapeutic response should include an assessment of the degree of intratumoral necrosis and reduction of the tumor mass. The fact is that RECIST does not include the evaluation of intratumor necrosis, which is required, but within this system, the evaluation of the effectiveness of therapy is performed by registering a decrease in tumor viability. If the presence of viable residual tumor tissue is verified on the control MDCT or MR examination, a repeat TACE procedure should be performed (30). In cases with locally advanced HCC patients should be aimed at treatment with systemic therapy (4, 7).

Risk of COVID-19 disease in patients with hepatocellular carcinoma and treatment strategy

In cancer patients, the risk of COVID-19 infection is 3 times higher than in the general population, and the risk of a severe form of the disease is increased by 5 times (32). On the other side, this is a heterogeneous group of patients with a difference in prognosis due to the malignant disease progression. Therefore, the risk of COVID-19 infection versus the potential benefit of treatment in every particular case should be estimated and discussed at the multidisciplinary tumor board and with the patient. Patient age, underlying liver disease and tumor-related factors (size, location, number of lesions, vascular invasion) as well as hospital resources should be considered when deciding on treatment strategy. Disease staging should be assessed by a multidisciplinary tumor board according to the BCLC criteria (33). Liver function should be assessed by taking into account serum concentrations of ALT, AST, GGT, alkaline phosphatase, total protein, albumin, total bilirubin as well as coagulation status (7). During the pandemic, each patient with HCC should undergo a rigorous individual risk-benefit assessment of available treatment options according to local expertise. Protocols of good clinical practice imply the application of so-called evidence-based medicine, which is still not possible in the context of COVID-19. In such circumstances, it is recommended to apply the experiences and knowledge gained from the period before the pandemic with certain modifications following the objective circumstances of the pandemic to prevent unwanted outcomes in the treatment of patients and at the same time maintain a high level of health care, with minimal delay in treatment. During the pandemic, one should not apply new and insufficiently tested treatment methods, new techniques or new materials, but optimize those procedures that are an integral part of local expertise (3). Also, each patient was carefully evaluated by a multidisciplinary team to define the appropriate treatment strategy, especially considering the risk of COVID-19 infection. The standards have been set for a rigorous assessment of the individual risk-benefit ratio of TACE within the current pandemic status and insufficient resources for all who could be treated.

Patients suffering from cancer represent a heterogeneous group in terms of prognosis, which depends primarily on the biological potential of the tumor, i.e. the rate of progression of the tumor disease. Therefore, in each individual case, the ratio of the risk of COVID-19 infection concerning the benefit of the treatment should be assessed and discussed at a conference (multidisciplinary) with the patient. For each patient with HCC, a rigorous risk-benefit assessment should be performed in relation to the available treatment methods. Factors related to the prevalence of COVID-19 infection, the risk of infection after treatment, and the necessity of hospital treatment after the TACE procedure should also be considered. Bearing in mind their immunosuppressive status, the risk of contracting a severe form of COVID-19 disease should be presented to patients with comorbidities (34).

Factors specific to COVID-19 should also be considered in terms of estimating the post-procedural infection risk and the need for hospitalization after TACE. Vascular interventions such as TACE are not aerosol-generating procedures and therefore carry the minimum risk of infection (5). The risk of infection should be discussed with patients having an underlying liver disease, diabetes or cardiovascular disease who have a higher possibility of adverse events due to the immunosuppressive states (34). The COVID-19 infection is proven to induce immune-mediated liver injury and hypoxemia (35, 36). Cancer treatment has a proven effect on the patient's immune system suppression, making them more vulnerable to infections, thus with higher morbidity and mortality related to COVID-19 infection (38). Most of those patients have associated comorbidities and liver disease which increases the risk of a severe form of COVID-19 disease (34). Thus maintaining cancer treatment while reducing the risk of COVID-19 infection must be balanced carefully (11).

Therefore, TACE represents the mainstay of BCLC B patient's treatment and could be used as a bridging therapy for other stages of the disease, although it is a palliative treatment with the objective to provide local tumor control as long as possible (3). The results from published studies have shown that in 19% of cases, TACE could be

performed even as an outpatient procedure (39) sparing the hospital resources. Depending on the tumor growth rate and response to the therapy repeated sessions are performed within 4 - 12 weeks (3). One of the major reasons to keep the patient at the hospital is to treat post-embolization syndrome which could be reduced by using a selective and super-selective approach while approaching the tumor-feeding vessel during embolization. Follow-up of patients after HCC treatment should be done according to the principle of maximizing the risk-benefit ratio (4). For patients with multinodular disease who did not have an adequate response after the second TACE treatment, which reduced the chances of achieving the desired therapeutic effect, the possibility of applying systemic chemotherapy should be considered (28). The treatment of these patients should be personalized, especially in terms of making decisions about the number and frequency of repeated TACE treatments, taking into account the objective circumstances of the organization of health services during a pandemic. In cases where it is not possible to provide a timely repeat TACE, the possibility of applying systemic chemotherapy should be considered (4).

Conclusion

During the pandemic, a principle of maximizing the risk-benefit ratio should be taken when evaluating the patient's eligibility for TACE in light of limited healthcare. Certain actions are required to reduce provider-related delays to improve timely diagnosis and treatment for patients with HCC. This guide could be a reference for the standardization of HCC treatment strategy in the light of pandemic's „distraction effect" and impending healthcare system collapse.

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