Review article

Current status of transarterial chemoembolization (TACE) agents in hepatocellular carcinoma treatment

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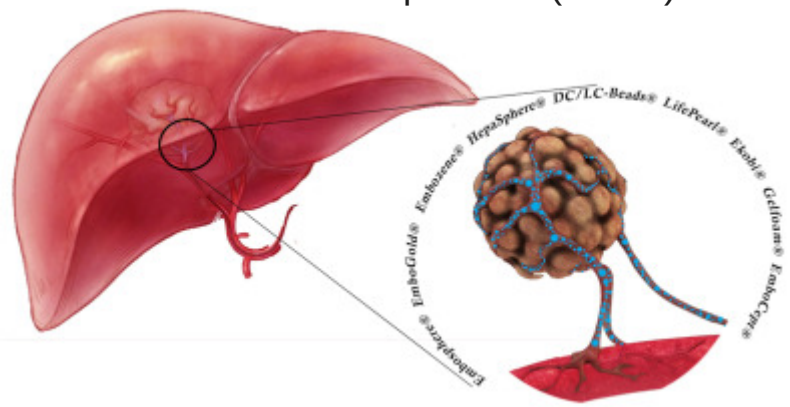
Abstract

Primary liver cancer is among the most common fatal solid cancers, ranking as the fourth most frequent cause of cancer-related mortality worldwide. Hepatocellular carcinoma (HCC) is the most prevalent

histological type of primary liver cancers, which accounts for up to 90% of cases and is resistant to a large percentage of currently available anti-cancer drugs. Amongst various therapeutic options, transarterial chemoembolization (TACE) is an efficient option in patients with the intermediate stage of HCC. Commercially, different embolients enable clinicians to perform TACE. Embolic materials include gelatin sponge, degradable starch microspheres (DSMs) and calibrated microspheres. This article reviews commercially available materials used in the TACE procedure and evaluates their pros and cons in this regard.

Graphical abstract

Transarterial chemoembolization (TACE) is an efficient option in patients with the intermediate stage of HCC. Commercially, different embolients enable clinicians to perform TACE. Embolic materials include gelatin Sponge, degradable Starch Microspheres (DSMs) and calibrated microspheres.



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Introduction

Primary liver cancer is among the most commonly fatal solid cancers, ranking as the fourth most frequent cause of cancer-related death worldwide [1]. It has been shown that the incidence rate of this cancer in both sexes and all ages will continue rising in the future [2,3].

Hepatocellular carcinoma (HCC) is the most prevalent histological type of primary liver cancer, which accounts for between 85% and 90% of cases and is resistant to a large percentage of currently available anti-cancer drugs. Over the past decades, the prevalence of HCC has been increasing in developed nations, especially in the USA [4]. It is reported that around 85% of HCC cases are mainly seen in developing nations, particularly in African countries and Eastern Asia [5].

The median age of HCC onset varies among the various regions of the world. For example, in Japan, Canada, the US, and European nations, the HCC most often occurs in individuals over 60 years. While, in Asia and most of Africa, HCC generally occurs in the age range 30–60 years [6]. Several studies have shown that there are some risk factors that may predispose to HCC, including viral infectious diseases (Hepatitis B virus (HBV) and Hepatitis C virus (HCV); the cause of 80% of HCC cases in the world) [7], fatty liver, chronic liver diseases, and diabetes [[7], [8], [9]], alcohol [6], aflatoxin and aristolochic acid [10], and obesity [8].

In addition, multiple observational studies have revealed that some non-pharmacologic (such as coffee) and pharmacologic (such as metformin, statins, and aspirin) agents play a protective role against the development of HCC [[11], [12], [13], [14]]. Despite lack of reliable evidence for the protective effect of these against cancers in randomized controlled trials (RCTs), consuming coffee is now suggested by the clinical practice guidelines for HCC in “European Association for the Study of the Liver (EASL)" [15].

In this article we have focused on transarterial chemoembolization (TACE) as a treatment modality for HCC and reviewed embolic systems, their characteristic, advantages and disadvantages.

According to the guidelines described by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), HCC can be diagnosed by imaging if the tumor mass size is larger than 10 mm. In addition, using either CT or MRI, arterial hyper-enhancement and venous washout in a cirrhotic liver can be identified [15,16].

Over the past 20 years, AFP (a known traditional biomarker) has been widely used as a diagnostic parameter. However, due to low sensitivity (40% of HCC patients have normal AFP level) [17] and low specificity (elevated plasma level of AFT is observed in other liver diseases, in addition to HCC), AFP was excluded from the diagnostic criteria in updated HCC guidelines presented by the AASLD (2010), EASL (2012), and NCCN (2014). Nevertheless, in many HCC guidelines published in Asia, such as APASL (Asian Pacific Association for the study of the Liver), AFP is yet known as an adjunctive and helpful surveillance parameter because it has been shown that AFP levels might accurately detect HCC patients with HIV infection and cirrhosis [18,19].

Metabolomics profiling is the comprehensive profiling of all low molecular weight compounds and metabolic alterations occurring in living systems and is now considered as an available strategy for detecting useful diagnostic biomarkers [20]. To date, in clinical practice, several metabolic-based biomarkers have been discovered for the diagnosis and prognosis of HCC [19]. Although metabolomics profiling has many advantages, its use for preventing HCC is yet in an early stage and has not achieved clinical use as a reliable strategy to detect high-risk patients with a 100% detection rate [20]. Further functional studies are needed to validate metabolomics profiling from research to clinical applications.

Clinical staging of HCC helps to evaluate the disease prognosis and treatment interventions. Table 1 indicates the most frequently used standard system named BCLC staging system.

Given that exacerbation of underlying liver disease may occur by most therapeutic methods, an inspection of tumor mass/extent and patient comorbidities and liver dysfunction severity should be taken into account by guideline. In various nations with different levels of specialty training and resources, there are highly variable treatment options. Therefore, obtaining new approaches in HCC treatment needs multidisciplinary and versatile strategies to achieve the best clinical outcome [21].

To date, there are 5 therapeutic approaches for management of HCC including surgical resection [22], transplantation [23], ablation (includes chemical ablations, thermal-based ablations and cryoablation) [24,25], systemic drug-based treatment (e.g. atezolizumab plus bevacizumab, regorafenib, sorafenib, and ramucirumab) [[26], [27], [28], [29], [30]], transcatheter tumor therapy (includes transarterial embolization (TAE), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE)) [31]. Table 2 shows the indications, advantages, and disadvantages of aforementioned treatment options.

In summary, choosing a valid guideline to achieve optimal treatment strategies, resources and income levels in countries should be considered. However, regardless of resource availability, targeted or immunotherapy should be considered for high-stage HCC. In patients with end-stage or terminal-stage HCC, supportive care is the mainstay of therapeutic strategy [54].

Not all therapeutic strategies are equally cost-effective and efficient in clinical practices, regardless of their financial burden. The curative treatment potentially should be used in the early-stage of HCC, while for

intermediate-stage HCC, the locoregional treatment would be the first choice. The locoregional therapy is used to reduce complications associated with other therapy procedures because it is directly localized to the tumor mass. All currently available therapeutic modalities can be applied to the tumor itself by this strategy. The standard procedures of locoregional therapy include percutaneous ethanol ablation (PEI), radiofrequency ablation (RFA), and transarterial chemoembolization (TACE) [55]. Nevertheless, these therapy procedures are resource-intensive that are being used in countries with high resources. It is worthy to note that sorafenib can be regarded as an alternative therapeutic modality in developing countries.

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  TACE is recommended for patients with BCLC stage B (evidence high; recommendation strong).

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  The utilize of drug-eluting beads has appeared comparable benefits to conventional TACE, and both can be used (evidence high; recommendation strong).

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  TACE is contraindicated in decompensated liver disease, advanced liver and/or kidney dysfunction, macroscopic vascular invasion, or extrahepatic spread (evidence high; recommendation strong).

- •
  There is insufficient evidence to recommend bland embolization, selective intra-arterial chemotherapy, and lipiodolisation (evidence moderate).

  Amongst various therapeutic options, TACE is an efficient therapy modality in the intermediate stage of HCC. The liver has a distinctive double blood supply, receiving 75% of its blood from the portal vein and the remaining 25% from the hepatic artery. Similarly, approximately three quarter of the required blood of the liver's normal parenchyma is supplied from the portal vein, and the hepatic artery provides the remaining one quarter. Liver tumors, however, receive the main part of the desired blood from the liver artery [56].

  TACE method is one of the first theranostic procedures applied in interventional radiology and includes a combination of diagnosis of liver tumors with tumor “tagging,” concurrent treatment, and evaluation of real-time therapy [57,58]. This method consists of two main steps of

cytotoxic drugs and embolization particles delivery into the branches of the artery feeding the tumor, resulting in ischemic tumor necrosis [59].

From femoral access and under fluoroscopic guidance, an accurate microcatheter is positioned into the targeted tumor-feeding artery. Iodinated contrast medium injection is carried out to depict the arterial anatomy and identifies targeted tissue areas to place the microcatheter into the vessels, and embolization of non-target normal liver parenchyma is avoided as much as possible. After selecting the injection site, the payload of “chemo"-"embolization” (chemotherapy drug + an embolizing agent) is injected [60]. Using the TACE method, highly concentrated doses of chemotherapeutic cytotoxic medicines are delivered to tumor mass, whereas the normal margin tissue of involved tissue is conserved. The embolic agents predispose tumor tissue to ischemia and necrosis and slow down the elimination of anti-cancer drugs.

However, because the blood flow from the portal vein is dominant, the blood supply to the normal parts of the liver organ is conserved [61]. Considering the mentioned benefits, TACE is the most frequently used method for preventing tumor progression among liver transplantation patients. Consistent with the above findings, randomized clinical trials (RTCs) in Europe and Asia have revealed that TACE increases the overall survival of patients with nonresectable HCC [59,61].

TACE consists of two methods: conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE). cTACE infuses a water-in-oil emulsion of cytotoxic agents and ethiodized oil (Lipiodol) into the branches of the artery feeding the tumor followed by embolizing the tumor blood vessels with embolic agents, while DEB-TACE injects chemotherapeutics loadable microspheres which selectively clog the vessels and allow controlled release of cytotoxic chemotherapy agents [62]. Doxorubicin, epirubicin, and cisplatin are among the most frequent cytotoxic drugs used in TACE [63].

In addition to the carrier ability of cytotoxic drugs, Lipiodol also has other theranostic benefits. It enables accurate real-time monitoring during emulsion delivery because of its radiopaque property. Furthermore, Lipiodol also has the distinctive property of being selectively up-taken by hyper-arterialized liver tumors, including HCC, and lasting for a long time [58,64]. However, cTACE has several drawbacks, including the drug's off-target release, the need for additional embolizing of the selected vessels, non-standardized preparation of emulsion, and drug release pharmacokinetics on drug release the type of emulsion. Therefore, to

overcome the above drawbacks, non-absorbable embolic microspheres (drug-eluting beads or DEBs) were developed over the past decades that have the ability to deliver drugs [62,65].

Several clinical investigations over the past years have reported the advantages of DEB-TACE over cTACE. For example, an investigation designed by PRECISION V. to compare the short-term clinical outcomes of DEB-TACE and cTACE. This study revealed that DEB-TACE correlated with improved tolerability compared to cTACE, with a considerable reduction in hepatotoxicity and cytotoxic drug-related complications [[66], [67], [68], [69]]. The PRECISION ITALIA investigation randomly categorized participants into cTACE or DEB-TACE groups and followed up for at least 24 months after TACE or until death. It has been shown that there is no statistically significant difference in overall survival rate between the studied groups; however, it was revealed that the DEB-TACE group significantly shows lower post-procedural pain [70]. The DEB-TACE group also exhibited complete or partial response (better objective response) [71].

Despite the investigated benefits of DEB-TACE, some studies show that clinical practice is still debating whether DEB-TACE is superior to cTACE in terms of overall survival and response to treatment [[72], [73], [74]].

Many drugs can be loaded into microspheres via absorption and ion exchange mechanisms. DEBs offer sustained release and tumor targeted drug delivery which prevents systemic distribution of cytotoxic drugs. Negatively charged commercial microspheres such as DC Bead® (BTG, London, UK), HepaSphere™ (Merit Medical, South Jordan, UT, USA), Oncozene™ TANDEM®(CeloNova BioSciences, Inc., San Antonio, TX, USA) and LifePearl® (Terumo European Interventional Systems, Leuven, Belgium) sequesters the cationic drugs like doxorubicin, epirubicin or irinotecan, through Coulomb charge interactions [75]. Many studies have compared pharmacokinetic profile of these drugs in DEB vs C-TACE. Gaba et al. have shown that both c-TACE and DEB-TACE acquired adequate cytotoxic doxorubicin level, but c-TACE had better tumor coverage in rabbit VX2 liver tumor model [76]. Varela and colleagues assessed that even with high dose injection of doxorubicin, DEB-TACE group C_{max} and AUC were remarkably lower than C-TACE [77] despite the fact that superiority of the DEB-TACE over C-TACE have not been established, DEB-TACE is more tolerable due to the elimination of the associated systemic chemotherapy toxicity [75].
Recent studies have developed novel drug delivery systems as an embolic and drug delivery agent. Yang et al. have developed in-situ

photopolymerizable semi-interpenetrating network (IPN) capable of cisplatin loading which exhibited prolonged and local drug delivery and suppressed tumor progression in orthotopic liver cancer mouse model [78]. Another study by Xinyi Li has developed magnetic hydrogel composing from polyvinyl alcohol, silica and iron oxide nanoparticle for increase in drug loading and sustainable release profile [79].

Cytotoxic drugs pharmacological effectiveness is lean on uptake and efflux transporters.

- 1
  Organic anion transporting polypeptides (OATP):
  OATP activity is affected by alteration of pH in tumor region [80]. This transporter is entryway for cytostatic drugs [14], such as irinotecan and its active metabolite, SN-38, paclitaxel, and several bile acid cisplatin conjugates (BAMET) [81,82].

- 2
  Organic cations transporters (OCT)*:*
  OCT uptake cationic compounds such as tyrosine kinase inhibitors which are novel approach in treatment of both HCC and cholangiocarcinoma [83].

- 3
  CTR family:
  CTR1 is proposed to be associated in the transport of drugs such as cisplatin.

  Another member of this family, named CTR2, is involved in cisplatin chemoresistance. So, CTR2 inactivation significantly increases the cisplatin tumor accumulation and its cytotoxic efficacy [84,85].

  This super family consists of breast cancer resistance protein, MRP2, P-glycoprotein or multidrug resistance protein, and BSEP. These transporters could be overexpressed in tumor cells so elimination of drugs increase and pharmacological efficacy decreases.

  Resistance to drugs such as irinotecan, anthracyclines, and cisplatin is induced by this efflux transporters [[86], [87], [88]].

  An increased expression of uptake transporters and a decreased expression of efflux transporters would favor the accumulation of cytostatic drugs within the tumor cells. Thus, patient-specific expression

of uptake and efflux drug transporters may contribute to the optimization of the selection of HCC drugs and/or adjustment of dosing.

Studies show that Median expression of MDR1, BCRP, MRP2 in HCC versus normal cells was lower, higher, and not changed, respectively [[89], [90], [91], [92]].

Also it has been shown that larger tumors expressed lower OCT and BCRP transporter levels. Sorafenib, which is systemic treatment choice for advanced-stage HCC is effluxed by BCRP. So it is suggested that patients with larger tumors may benefit from treatment with sorafenib [91,93].

Section snippets

Embolic materials

Commercially, there are different embolients that enable clinicians to perform TACE. Table 3 summarizes the available commercial products, of which some of them are briefly explained in the following sections. Table 4 provides a summary of some of the most frequently used embolic materials in this area which includes different types of material like polymers (PVA, PLGA, PCLA, PEGMA, …), polysaccharides (chitosan, cellulose, …), gelatin, and etc. Table 5 introduces clinical applications of TACE

Conclusion

Over the past years, considering the development of radiopaque beads which can load antiangiogenic and cytotoxic drugs, five essential outcomes can be achieved: 1) Tracing of the DEBs in the body, 2) Inducing the ischemic necrosis in a tumor, 3) Suppressing the tumor defensive mechanisms, in which angiogenesis process, under the influence of antiangiogenic drugs, is inhibited, 4) Releasing the chemotherapeutics cytotoxic drugs in the tumor site and reducing the risk of systemic complications 5)

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

None.