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EDITORIAL

Enhancing global hepatocellular carcinoma management: Bridging Eastern and Western perspectives on dexamethasone and N-acetylcysteine before transarterial chemoembolization

Thang Viet Luong, Nam Van Duc Nguyen, Linh Duy Le, Hieu Nguyen Hoang Minh, Hai Nguyen Ngoc Dang

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Thang Viet Luong, Nam Van Duc Nguyen, Linh Duy Le, Department of Internal Medicine, University of Medicine and Pharmacy, Hue University, Hue 530000, Viet Nam

Hieu Nguyen Hoang Minh, Department of Diagnostic Imaging, University of Medicine and Pharmacy, Hue University, Hue 530000, Viet Nam

Hai Nguyen Ngoc Dang, Faculty of Medicine, Duy Tan University, Da Nang 550000, Viet Nam

Co-first authors: Thang Viet Luong and Nam Van Duc Nguyen.

Corresponding author: Hai Nguyen Ngoc Dang, MD, Doctor, Lecturer, Researcher, Faculty of Medicine, Duy Tan University, No. 254 Nguyen Van Linh, Da Nang 550000, Viet Nam.
ngochai123dc@gmail.com

Abstract

This article explores the integration of Eastern and Western perspectives on the use of dexamethasone and N-acetylcysteine as premedications in transarterial chemoembolization for hepatocellular carcinoma (HCC). By examining key concerns raised by Western researchers, particularly regarding the different etiologies of liver cirrhosis, and contrasting them with robust clinical data from Asia, this article highlights the necessity for region-specific research and proposes future directions for global HCC management.

Key Words: Hepatocellular carcinoma; Transarterial chemoembolization; Dexamethasone; N-acetylcysteine; East-West perspectives; Post-embolization syndrome

Core Tip: This editorial presents a critical assessment of the integration of dexamethasone and N-acetylcysteine in transarterial chemoembolization for hepatocellular carcinoma by juxtaposing Eastern and Western perspectives. It emphasizes the need for tailored treatment protocols that consider regional differences in disease etiology and healthcare practices, ensuring optimal patient outcomes across diverse populations.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most significant global cancers, with its prevalence and underlying causes varying markedly between regions[1]. In Asia, chronic hepatitis B virus infection remains the primary cause of liver cancer. By contrast, Western countries have a higher incidence of HCC due to metabolic disorders and alcohol-related liver disease. However, these factors are also increasingly contributing to HCC cases in Asia[2]. These differences in etiology not only affect the clinical presentation and progression of HCC but also influence the management strategies employed.

Transarterial chemoembolization (TACE) has become a cornerstone in the treatment of intermediate-stage HCC, particularly for patients who are not candidates for surgical resection or liver transplantation. However, TACE is associated with several complications, including post-embolization syndrome (PES), acute liver failure, acute kidney injury, and liver abscesses. The incidence of major complications ranges from 4% to 7%, with PES being the most common, affecting 90% of patients and negatively impacting treatment outcomes[3]. Optimizing premedication protocols is essential to improve these outcomes.

Recent research in Asia has shown promising results with the use of dexamethasone (DEXA) and N-acetylcysteine (NAC) as premedications to mitigate PES[4]. DEXA is a steroid hormone, specifically a potent glucocorticoid, that has anti-inflammatory, immunosuppressive, detoxifying, and shock-resistant effects. This hormone acts on its target receptor, the glucocorticoid receptor. With its potent anti-inflammatory and immunosuppressive effects, DEXA inhibits the release of inflammatory mediators and certain cytokines. Furthermore, it promotes apoptosis in immune cells, thereby helping to mitigate sterile inflammation that can arise following TACE[5,6]. Several studies have suggested that DEXA is effective in preventing nausea and vomiting in patients after surgery or procedures such as TACE, primarily due to its anti-inflammatory properties and reduction of arachidonic acid secretion[7]. NAC is considered an intracellular cysteine that enhances glutathione synthesis and exhibits strong antioxidant and anti-inflammatory effects[8]. Beyond its established role in treating acetaminophen overdose, NAC effectively protects the liver from non-acetaminophen agents by enhancing hepatic tissue perfusion, ensuring adequate oxygen supply, and reducing liver damage caused by inflammation and apoptosis[9,10].

Although several studies have demonstrated the benefits of DEXA and NAC in preventing PES after TACE, the applicability of these findings varies by region due to differences in disease etiology, healthcare practices, and patient demographics. A recent (2024) editorial by Biolato and Pompili[11] provides a Western perspective on the use of DEXA and NAC in TACE, emphasizing potential risks and advocating for caution when translating these findings to Western populations.

This article aims to critically assess and integrate insights from both Eastern and Western perspectives, building on the foundation laid by Biolato and Pompili[11], to propose a more globally relevant approach to HCC management.

WESTERN PERSPECTIVE

Biolato and Pompili's Editorial[11] highlights several critical considerations specific to the Western context, where different etiological factors shape the landscape of HCC management compared to Asia. In the West, the increasing prevalence of metabolic syndrome and alcohol-related liver disease has shifted the primary causes of liver cirrhosis, with these factors now surpassing viral infections as the leading causes of HCC[2,12,13]. This shift has significant implications for pre-TACE prophylactic protocols, particularly high-dose DEXA. This can be explained by the fact that viral hepatitis causes more intense inflammation compared to liver damage from alcohol or metabolic diseases, and the inflammatory response may be more severe following PES[14]. DEXA, tested in clinical trials, demonstrates significant anti-inflammatory effects by reducing tissue inflammation through the inhibition of inflammatory cell and mediator accumulation at glucocorticoid receptors, stabilizing lysosomal cell membranes to prevent the release of enzymes and mediators, and maintaining vascular permeability[15]. DEXA's efficacy in reducing nausea and vomiting has been proven to prevent PES across a range of other surgical procedures[15,16]. It is apparent that using DEXA for PES prophylaxis after TACE is more effective in patients with HCC due to viral hepatitis. Additionally, variations in the prevalence of HCC etiology across different regions affect both clinical perspectives and treatment strategies.

One of the primary concerns raised by Biolato and Pompili[11] is the potential exclusion of patients with type 2 diabetes or hypertension from DEXA protocols due to the risk of worsening hyperglycemia. Hyperglycemia complicates the management of these comorbid conditions and potentially interferes with the inflammatory-mediated tumor response, which is critical for the effectiveness of TACE[11]. The authors argue that this risk is particularly pronounced in Western populations, where metabolic disorders are more prevalent.

Additionally, Biolato and Pompili[11] emphasized that the choice of TACE technique differs between regions. In Western countries, drug-eluting bead TACE (DEB-TACE) is more commonly used than conventional TACE (cTACE), which is prevalent in Asia[11]. DEB-TACE is associated with a lower incidence of PES, raising questions about the necessity and efficacy of premedications such as DEXA and NAC in these patients[17]. The lower PES rates in DEB-TACE could potentially reduce the perceived benefits of such prophylactic treatments, leading to a different risk-benefit analysis in Western clinical practice.

These considerations underscore the importance of context when applying clinical findings across regions with differing disease etiologies and treatment practices. The Western perspective rightly calls for caution in blanket application of Eastern research findings without adapting them to the specific needs and risks of Western patient populations. However, this also opens the door to further investigation into how these risks manifest in Eastern populations and whether similar concerns should be raised there.

COMPLEMENTARY CHEMOTHERAPEUTIC AGENTS AND THE ENHANCED ROLE OF DEXA AND NAC

In addition to DEXA and NAC, several other drugs are used in TACE. Notably, cyclooxygenase-2 (COX-2) inhibitors and opioids are employed to manage post-TACE pain. While opioids are highly effective for pain relief, COX-2 inhibitors are generally recommended over opioids due to concerns about the side effects and addictive potential of opioids. Furthermore, COX-2 inhibitors offer the advantage of both analgesic and anti-inflammatory effects, helping to reduce the need for opioid use[18]. Second, antiemetic drugs are recommended by the American Society of Clinical Oncology, including DEXA, 5-HT3 receptor antagonists, and aprepitant, to combat chemotherapy-induced nausea and vomiting [19]. Third, there are other types of steroids besides DEXA. Additionally, there are several drugs that treat the symptoms of PES syndrome. Compared to other steroids, DEXA has a longer biological half-life and a more substantial effect (Table 1)[20]. Compared to COX-2 inhibitors, DEXA has a more potent and broader anti-inflammatory effect, acting on various pro-inflammatory factors (IL-1, IL-6, and tumor necrosis factor alpha). Furthermore, DEXA can penetrate the blood-brain barrier, potentially reducing the risk of inflammation-induced tissue damage[21]. Therefore, enhancing the use of DEXA can alleviate both symptoms, such as nausea, vomiting, pain, and fever, and elevated alanine aminotransferase, and also exert a potent anti-inflammatory mechanism to prevent PES[22]. NAC has been shown to protect liver cells from damage caused by chemical exposure and ischemia-reperfusion injury[23]. NAC helps protect liver cells from the damage induced by embolization and chemotherapy that can occur after TACE, thereby promoting liver function recovery.

CRITICAL ANALYSIS

The concerns raised by Biolato and Pompili[11] are crucial for understanding the broader implications of applying Eastern clinical findings to Western settings. Their focus on the potential risks associated with high-dose DEXA, particularly in populations with prevalent metabolic disorders, underscores the need for careful patient selection and monitoring. Hyperglycemia, a known side effect of DEXA, is of particular concern in Western populations, where diabetes and metabolic syndrome are common comorbidities. This risk is compounded by the possibility that hyperglycemia could interfere with the inflammatory-mediated tumor response, potentially diminishing the effectiveness of TACE.

However, these concerns should not overshadow the promising results from Eastern studies. Randomized controlled clinical trials in Thailand involving 100 patients found that the incidence of PES was significantly lower in the group receiving the combined therapy of DEXA + NAC, with rates of 6% and 80%, respectively ($P < 0.001$)[4]. Another study in South Korea found that the use of DEXA helps reduce the incidence of PES and shorten hospital stays after TACE[22]. In addition, a retrospective analysis conducted in Japan aimed at evaluating the effects of DEXA in preventing PES found that DEXA can significantly reduce the incidence of PES after TACE, demonstrating high efficacy and safety[15]. In China, a randomized, double-blinded, and controlled trial involving 120 patients demonstrated that the combination of DEXA and ginsenosides helps in preventing and treating PES[24]. Research conducted in Asia has shown the efficacy of DEXA and NAC in reducing PES, particularly in patients undergoing cTACE, which remains the standard in many Asian countries. The benefits observed in these studies, such as reduced incidence and severity of PES, are significant and suggest that these premedications can play a crucial role in improving patient outcomes.

The differing disease etiologies between Eastern and Western regions suggest that a one-size-fits-all approach may not be suitable. Unlike the Eastern focus on viral hepatitis, the Western emphasis on metabolic liver disease and alcohol-related liver disease raises valid concerns. However, viral hepatitis, particularly of hepatitis C virus, remains an important cause, accounting for a significant proportion of HCC cases in the West[25]. Consequently, the application of DEXA for PES prophylaxis following cTACE should continue to be evaluated in Western countries. This difference in etiology may influence the side effects and overall effectiveness of DEXA, necessitating further research to determine how these factors play out in different populations. In addition to diabetes and hypertension, certain side effects and contraindications of DEXA, such as systemic fungal infections, active gastric ulcers, cerebral malaria, and hepatotoxicity, could impact treatment decisions[6]. However, it is important to note that most of these adverse effects are generally not associated with the use of a single dose of DEXA for PES prophylaxis following TACE[26]. Although previous studies have not reported adverse effects of DEXA for PES prophylaxis following TACE, differences in disease etiology may still impact treatment efficacy and the occurrence of unwanted side effects in patients. Therefore, further research is needed to identify the factors affecting treatment based on regional differences in disease etiology, as well as to evaluate any

Table 1 Corticosteroid comparison chart

	Equivalent glucocorticoid dose (mg)	Potency relative to hydrocortisone		Half-life	
		Anti-inflammatory	Mineralo-corticoid	Plasma (minutes)	Duration of action (hours)
Glucocorticoids					
Short acting					
Hydrocortisone	20	1	1	90	8–12
Cortisone acetate	25	0.8	0.8	30	8–12
Intermediate acting					
Prednisone	5	4	0.8	60	12–36
Prednisolone	5	4	0.8	200	12–36
Triamcinolone	4	5	0	300	12–36
Methyl-prednisolone	4	5	0.5	180	12–36
Long acting					
Dexamethasone	0.75	30	0	200	36–54
Betamethasone	0.6	30	0	300	36–54
Mineralo-corticoids					
Fludrocortisone	0	15	150	240	24–36
Aldosterone	0	0	> 400	20	-

potential adverse effects associated with the use of DEXA.

Another issue related to cultural characteristics in the East that may affect the efficacy of DEXA and NAC is the use of traditional medicine by patients, the therapeutic effect may vary depending on the type of drugs used and their method of combination. A study by Oh *et al*[27], which evaluated the adjunctive effects of traditional medicine on TACE therapy in 2623 patients in Korea, demonstrated improvements in overall survival rates at 0.5 years, 1 year, 2 years, and 3 years. This combination therapy also increased the tumor response rate. However, no studies have evaluated the interactions between DEXA and NAC with herbal medicine in the prevention of PES and in supporting TACE treatment outcomes. Therefore, additional studies on the interactions between these medications are necessary to support the management and treatment of TACE in patients with HCC.

In the treatment of HCC with TACE, in addition to the ambiguity regarding differences in therapeutic efficacy, the choice between cTACE and DEB-TACE for treating small HCC (< 2 cm) remains debated. In such cases, relatively intact vascularity diminishes the effectiveness of TACE using both methods, and recurrence rates after DEB-TACE have been reported to be higher compared to cTACE[28,29]. Additionally, the selection of prophylactic agents before TACE must consider their advantages and disadvantages to determine the most suitable option for the patient. Although doxorubicin is a widely used agent for PES prophylaxis following TACE, particularly DEB-TACE, it is important to recognize that it is also a known cause of hepatic artery damage-a complication with a high incidence following DEB-TACE[28].

There are currently no specific guidelines for deciding between cTACE and DEB-TACE. The choice of treatment method depends on specific circumstances, including issues related to cost, undesirable effects, systemic toxicity, hepatic toxicity, the ability to prevent PES, the efficacy of chemotherapy agent release, and tumor size, all of which can impact treatment effectiveness[16,28-31]. We have summarized these issues in Figure 1.

BRIDGING THE EAST-WEST DIVIDE

Certain differences in treatment perspectives between the East and the West stem from various factors related to the characteristics of each region. We have briefly listed these factors in Figure 2. Bridging the gap between Eastern and Western perspectives on TACE is crucial for addressing the diverse needs of different regions. This involves thoroughly analyzing existing research and creating tailored treatment protocols that account for the unique challenges patients face in each region. By thoughtfully integrating robust Asian data with the cautious approach emphasized in Western studies, we can develop comprehensive guidelines that maximize the benefits of DEXA and NAC while minimizing potential risks.

One potential avenue for bridging this divide is through multinational clinical trials that evaluate the long-term effects of these premedications in diverse populations. Such trials could help to identify which patients are most likely to benefit from DEXA and NAC and which may be at increased risk of adverse effects. By tailoring treatment protocols to the

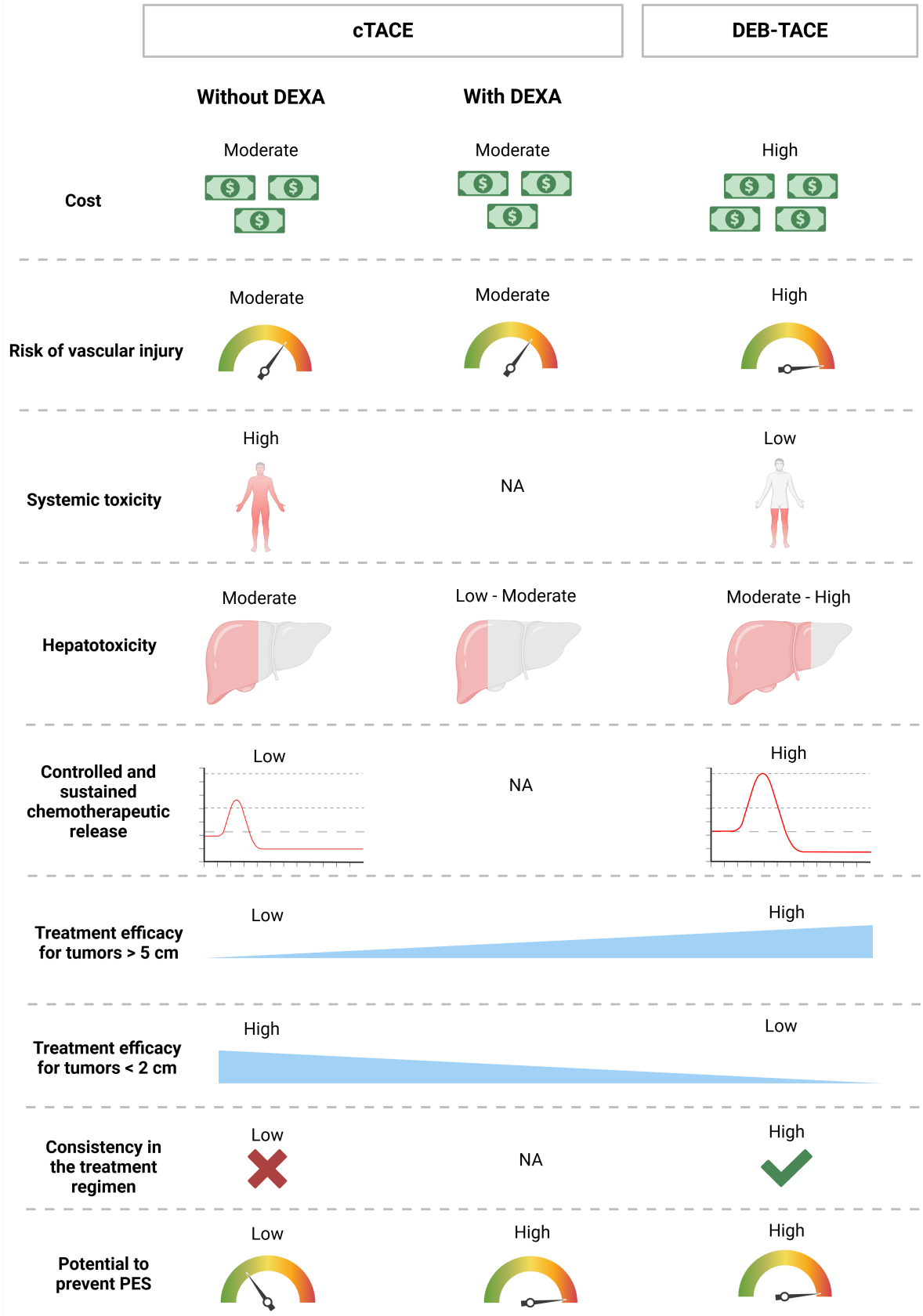

Figure 1 Comparison between conventional transarterial chemoembolization, conventional transarterial chemoembolization with dexamethasone prophylaxis, and drug-eluting bead transarterial chemoembolization. The cost of treatment with conventional transarterial chemoembolization (cTACE) and drug-eluting bead TACE (DEB-TACE) is not significantly different; However, DEB-TACE is generally more expensive. The use of cTACE, with or without prophylactic dexamethasone (DEXA), reduces the risk of vascular damage in the liver more effectively than DEB-TACE, which is associated with the chemotherapeutic agent doxorubicin. The systemic toxicity of cTACE is higher compared to DEB-TACE; however, hepatic toxicity is lower with cTACE. The use of DEXA for prophylaxis further reduces liver damage due to inflammation. DEB-TACE has the advantage of drug release and maintenance, which is a significant

benefit that cTACE lacks, leading to higher agreement on the use of DEB-TACE. The efficacy of the two methods in treating tumors varies based on size, with DEB-TACE showing better treatment outcomes for tumors larger than 5 cm. However, for tumors smaller than 2 cm, the effectiveness may not be clear and could even be lower for DEB-TACE compared to cTACE. The ability to prevent post-embolization syndrome (PES) is higher with DEB-TACE. Similarly, cTACE can effectively prevent PES when prophylaxed with DEXA. NA: Not available; DEB-TACE: Drug-eluting bead transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization; DEXA: Dexamethasone.

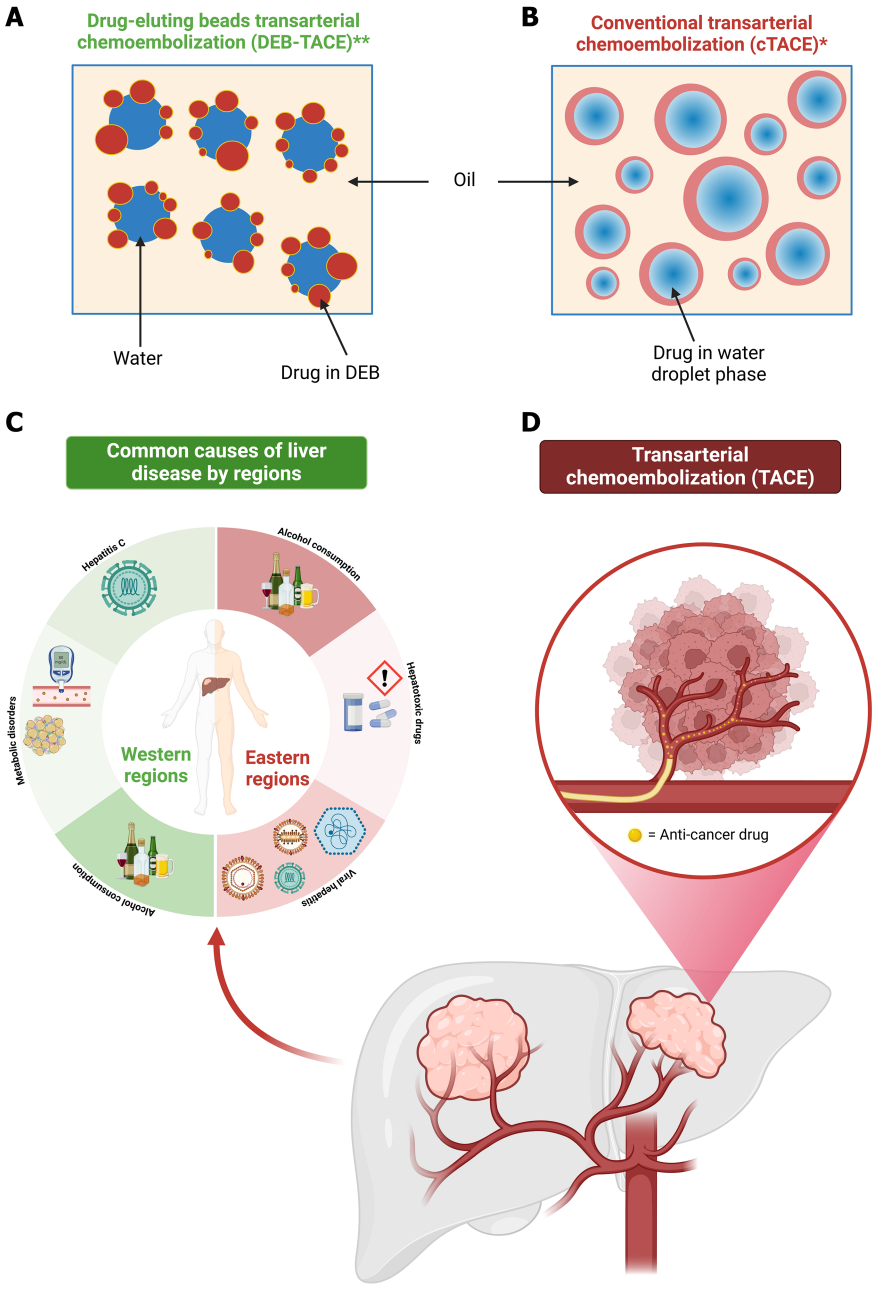

Figure 2 Differences in treatment perspectives. A: Drug-eluting bead transarterial chemoembolization (TACE) is more favored in Western countries; B: Conventional transarterial chemoembolization is more favored in Eastern countries.; C: Describe the common causes of liver disease in the Western and Eastern regions, where the group of causes for liver disease in the West includes hepatitis C virus, alcohol-related liver disease, and metabolic-related liver disease, while in the East it includes viral hepatitis in general, use of hepatotoxic drugs, and alcohol consumption; D: Indications for TACE treatment in liver cancer patients. DEB-TACE: Drug-eluting bead transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization.

specific needs of different populations, we can ensure that all patients receive the most effective and safe care possible.

Furthermore, collaboration between Eastern and Western researchers could lead to the development of new strategies that incorporate the strengths of both regions' approaches. For example, the integration of DEB-TACE into Asian treatment protocols could potentially reduce the incidence of PES, while the inclusion of DEXA and NAC in Western protocols could enhance patient outcomes in certain populations. Cross-regional collaboration is essential for advancing the global management of HCC.

FUTURE RESEARCH DIRECTIONS

Prospective cohort studies or longitudinal follow-ups are urgently needed to evaluate the long-term effects of DEXA on tumor response and survival rates post-TACE, particularly in populations with a high prevalence of diabetes and metabolic disorders. Such research would be invaluable in weighing the risks of hyperglycemia and hypertension against the benefits of reduced PES. Furthermore, conducting multinational trials with diverse, population-specific data will enhance the specificity of treatment approaches. These trials must consider variations in liver disease etiology, demographic factors, and healthcare infrastructure. Comparative studies are essential to objectively assess the impact of cultural differences, such as dietary practices and traditional medicines in Asian populations, on the interactions with DEXA and NAC. Ultimately, this comprehensive understanding will facilitate the optimization of treatment protocols tailored to individual patients, ensuring the best therapeutic outcome.

CONCLUSION

While the Western perspective highlights valid concerns regarding DEXA and NAC in TACE, integrating these insights with robust Asian data is crucial. Collaborative efforts between Eastern and Western researchers will enable the creation of treatment protocols that are both effective and culturally attuned. This strategy promises to enhance global HCC management and improve patient outcomes worldwide.

FOOTNOTES

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ORCID number: Thang Viet Luong 0009-0008-5109-9115; Nam Van Duc Nguyen 0009-0003-8558-9933; Linh Duy Le 0009-0001-8442-1288; Hieu Nguyen Hoang Minh 0009-0000-5909-9939; Hai Nguyen Ngoc Dang 0009-0006-4512-4658.

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