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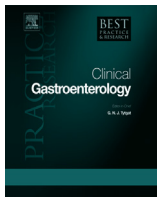

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Chemoembolization and radioembolization

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A B S T R A C T

Chemoembolization and radioembolization are at the core of the treatment of patients with hepatocellular carcinoma who cannot receive potentially curative therapies such as transplantation, resection or percutaneous ablation. They differ in the mechanism of action (ischaemia and increase cytotoxic drug exposure for chemoembolization, internal irradiation for radioembolization) and may target different patient populations. Chemoembolization with cytotoxic drug-eluting beads is a more standardized although not necessarily more effective way of performing chemoembolization. Cytoreduction is achieved in most patients but complete tumor ablation may be achieved and lead to extended survival. Grade 1 level of evidence support the use of chemoembolization for the treatment of patients in the early and intermediate stages while grade 2 evidence supports the use of radioembolization for the treatment of patients in intermediate to advanced stages. Selecting the best candidates for both techniques is still a work in progress that ongoing clinical trials are trying to address.

Introduction

Most patients with hepatocellular carcinoma (HCC) are diagnosed at late stages, when curative surgical treatments cannot be applied [1]. According to guidelines from the European and American Association for the Study of the Liver [2,3], the BCLC classification with its five tumor stages should be

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used for tumor staging. Surgery by means of resection or transplantation and percutaneous ablation are restricted to the very early or early tumors (stage 0 and A) while intraarterial and systemic therapies are recommended for intermediate and advanced tumors, respectively (stages B and C) [4]. However, up to 50% of patients cannot receive the recommended treatment modality because of availability, technical issues, age or comorbidities [5] and guidelines are evidence-based flexible frameworks on which individual therapeutic strategies can be built upon by multidisciplinary teams [2]. The most common intraarterial techniques used in HCC treatment are transarterial chemoembolization (TACE) with or without drug-eluting beads (DEB) and radioembolization (RE). They differ in mechanism of action, technique and typical patient population, which translates into differences in patient monitoring, complications and outcomes. And they are all widely accepted for treating appropriately selected HCC patients.

Chemoembolization

Conventional procedures

TACE comprises different procedures intended to increase the exposure of tumor cells to cytotoxic agents, and to induce ischemic necrosis. In conventional TACE this is accomplished by the sequential intra-arterial injection of chemotherapeutic agents mixed with Lipiodol and embolizing particles. The wide variety of drug vehicles, cytotoxic agents and embolizing particles available has introduced numerous variations worldwide. Emulsification in Lipiodol is believed to increase intratumoral retention of the cytotoxic agents although all drugs used (doxorubicin, mitomycin C, doxorubicin and cisplatin) are highly hydrophilic. This is followed by embolization of the target vessels with gelfoam, which is very heterogeneous in size, or the more recently calibrated polyvinyl alcohol or acrylic copolymer gelatin particles. The use of calibrated particles is increasing worldwide since they can be chosen by size according to the target vessel [6].

The place where the tip of the catheter is placed and the degree of blood flow stasis achieved determine the volume of non-tumoral liver that is involved and the degree of dearterialization, and thereby influence the final outcome. Superselective catheterization and complete stasis are recommended to maximize the benefit. Complete responses are rarely seen after a single session of conventional TACE and repeated sessions can be scheduled at fixed pre-planned intervals or depending on the observed response. This ‘on demand’ approach to repeated TACE is recommended nowadays because of its more favourable safety profile [7]. Patients are thus evaluated every 6–8 weeks and additional TACE sessions are performed only if contrast-enhanced areas revealing tumor activity are observed in cross-sectional imaging.

Conventional TACE is largely a safe procedure frequently followed by side effects that can be occasionally severe. The most common (>40% of patients) is the post-embolization syndrome, consisting of mild and transient nausea, abdominal pain and fever. A transient decline in liver function is common but acute liver decompensation (ascites, encephalopathy or jaundice) is reported in only 0.1–3% of procedures [8,9]. Biliary and gastrointestinal complications have been reported in 2–10% [10] and 1–5% [11] of patients, respectively. Other complications include liver abscesses in patients with incompetent ampulla [12], vascular injury from repeated intraarterial chemotherapy [13], and tumor rupture [12]. Mortality rates range widely from 0.003 to 10% in the different series [14,15] but when the appropriate patients and procedures are selected, conventional TACE is a highly safe technique.

The evidence that supports the use of conventional TACE for unresectable HCC is two randomized controlled trials in selected patients with preserved liver function [16,17]. Three meta-analyses [14,18,19] have afterwards confirmed that conventional TACE improves survival of unresectable HCC patients. According to Western guidelines, TACE is indicated in HCC patients in the intermediate stage, i.e., those with multinodular HCC, relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread [3]. However, around half of the patients recruited in the two positive trials were likely patients in the early stage in which ablation was deemed unfeasible. In fact, the range of patients treated by TACE in clinical practice largely exceeds the boundaries of the intermediate stage (Table 1) and reported survivals widely range from 8 to 26% at five years [15,20–24].