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Trans-arterial chemoembolization as a therapy for liver tumours: New clinical developments and suggestions for combination with angiogenesis inhibitors

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Abstract

The liver is the primary site of metastases for many malignancies. Gastrointestinal cancers are especially prone to spread to the liver and other tumours, as breast cancer and melanoma often spread to the liver. On the other hand, hepatocellular cancer (HCC) is the fifth most common malignancy in the world due to its common etiology from chronic liver damage caused by hepatitis or cirrhosis. Treatments of liver tumours vary according to histology and liver invasion and until now trans-arterial chemoembolization (TACE) has represented a main approach in the therapy of liver tumours. This review takes into consideration: (i) the background to utilizing TACE in liver tumours; (ii) TACE methods and the biological rationale for utilizing chemotherapeutic agents coated to a new micro-particle such as DC-Beads and HepaSphere; (iii) clinical experiences employing TACE in different liver tumours; (iv) the pivotal role of angiogenesis and hypoxia-induced angiogenesis following TACE with special references to HCC. Finally, the rationale for the combination of TACE with angiogenesis inhibitors is also discussed.

Keywords: Trans-arterial chemoembolization (TACE); Liver tumours; DC-Beads; HepaSphere; Doxorubicin; Irinotecan; VEGF; Angiogenesis; Angiogenesis inhibitors

1. Background

Regional intra-arterial infusion therapy is often used clinically in patients with primary and secondary tumours of the liver because liver tumours, unlike healthy liver tissue, are supplied almost exclusively by hepatic arterial flow [1]. Tumour extraction of several anti-tumoural drugs, such as doxorubicin, mitomycin and 5-fluorouracil and irinotecan, is higher when administered during trans-arterial chemoembolization (TACE) [2]. Classical TACE involves the emulsification of a chemotherapeutic agent in an oily medium, used in this case as a drug carrier, which is delivered intra-arterially to liver tumours for maximum effect. The purpose of embolization is to reduce arterial inflow, diminish washout of the chemotherapeutic agent, and prolong contact time between cancer cells and the chemotherapeutic agents [3]. However, despite evidence of some clinical success with TACE, the search for more effective drug delivery systems persists. Chemoembolization with drug-eluting beads combines the drug with the embolization device by using the embolic device to reduce blood flow to the tumour whilst at the same time eluting a chemotherapeutic agent into the tumour via its own vasculature. Therefore, beads with the capability to elute drugs may offer the possibility to control precisely the release and dose of the chemotherapeutic agent into the tumour bed.

2. Embolic agents

2.1. Lipiodol as a classical embolic agent

Lipiodol (iodized oil; Guerbet Laboratories, Roissy, France), an iodinated ethyl ester of poppy seed oil, is an oily contrast medium and has been used for lymphangiographic studies. The use of TACE to treat hepatocellular cancer (HCC) really began after lipiodol was introduced as a drug carrier and an embolic agent in the early 1980s [4]. When injected into the hepatic artery, lipiodol selectively remains in tumour nodules from several weeks to over a year due to a siphoning effect from hypervascularization of the tumour vessels and an absence of Kupffer cells inside tumour tissues. This results in embolic effects on smaller vessels [5]. Lipiodol has another role as a vehicle to carry and localize chemotherapeutic agents inside a tumour. Anticancer drugs used in conjunction with Lipiodol include doxorubicin, epirubicin, aclarubicin, 5-fluorouracil, mitomycin and cisplatin [6]. The anticancer drugs are vigorously mixed with the lipiodol through the use of a pumping method to prepare an emulsion, and when the emulsified lipiodol and drug mixture is injected into a tumour supplying vessels, the anticancer drug is slowly released from lipiodol and remains in high concentrations within the tumour for a prolonged period [7,8].

Other experimental data suggest the use of a doxorubicin–lipiodol–gelfoam combination to provide the best therapeutic effect [9]. This data implied that gelfoam embolization functions by releasing doxorubicin more slowly from lipiodol, hence further increasing the drug concentration inside the tumour by preventing washout of the emulsion as well as increasing the embolization effect. Though the use of lipiodol in TACE has been challenged, there is substantial evidence that confirms the efficacy of its use. Lipiodol is still widely adopted in TACE protocols [10].

2.2. Other embolic agents used

Commonly used embolic agents include gelatin sponges, polyvinyl alcohol particles and microspheres. The use of steel