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• REVIEW •

Combined interventional therapies of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, responsible for an estimated one million deaths annually. It has a poor prognosis due to its rapid infiltrating growth and complicating liver cirrhosis. Surgical resection, liver transplantation and cryosurgery are considered the best curative options, achieving a high rate of complete response, especially in patients with small HCC and good residual liver function. In nonsurgery, regional interventional therapies have led to a major breakthrough in the management of unresectable HCC, which include transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave coagulation therapy (MCT), laser-induced thermotherapy (LITT), etc. As a result of the technical development of locoregional approaches for HCC during the recent decades, the range of combined interventional therapies has been continuously extended. Most combined multimodal interventional therapies reveal their enormous advantages as compared with any single therapeutic regimen alone, and play more important roles in treating unresectable HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly malignant tumour with a very high morbidity and mortality, carrying a poor prognosis and presenting considerable management[1]. The treatment of patients with HCC has been evolving in the past years.

Liver resection remains a good treatment for HCC in patients with cirrhosis[2]. The best results are obtained in patients with small, non-invasive tumours[3]. However, only a small number of patients are suitable for curative resection due to many factors such as multicentric tumours, extrahepatic metastases, early vascular invasion, coexisting advanced liver cirrhosis and comorbidities[4,5]. Liver transplantation seems to be the choice for monofocal HCC less than 5 cm in diameter and in selected cases of plurifocal HCC[6], but may be limited by availability of donor organs and a long waiting time[7-9]. Cryosurgery destroys neoplastic tissue by application of cold and affords a better chance of cure because of predictable necrosis even for HCC larger than 3 cm, but its use is limited by a high complication rate[10].

Local methods for tumour ablation, which include transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), microwave coagulation therapy (MCT), laser-induced thermotherapy (LITT), are promising extensions of tumour therapy, especially in patients with limited liver function, unresectable tumours, or multifocal tumours[11]. Since TACE was introduced as a palliative treatment in patients with unresectable HCC, it has become one of the most common forms of interventional therapy[12-15]. TACE has been shown to reduce systemic toxicity and increase local effects and thus improve the therapeutic results[14, 16]. However, its perceived benefit for survival has not been substantiated in randomized trials, presumably because its anticancer effect is offset by its adverse effect on liver function. Its therapeutic effect is also limited by the lack of appropriate and reliable embolic agents and when the tumour is infiltrative in nature or is hypovascular, too large or too small[17-19]. PEI is widely used with excellent results for small, encapsulated tumours in livers with less than three HCCs, but it is not suitable for patients having coagulopathy or ascites[19]. While RFA results in a higher rate of complete necrosis and requires fewer treatment sessions than PEI, the complication rate is higher with RFA than with PEI[20]. MCT under local anaesthesia is a minimally invasive and effective therapy when carried out on a single occasion to treat HCC located near the liver surface[21]. MCT may be superior to PEI for the local control of moderately or poorly differentiated small HCC[22, 23]. MR-guided LITT is another local effective therapy with low morbidity in malignant liver tumours with a maximum quantity of 5 and a size of < or = 5 cm[24,25], but local recurrence can occur even in small HCC, while this drawback is infrequent[26]. Biotherapy will play a certain role in the treatment of HCC, however, the results are still controversial[27].

It is well known that improving the overall therapeutic effects of liver cancer depends on the combined therapies. The purpose of combined interventional therapies for HCC is to give full play to the merits of various therapeutic schemes, to overcome their shortcomings and to get combined effects that are impossible to obtain from any single therapeutic regimen. The general principles of combined interventional therapies for HCC are to destroy the tumour as completely as possible, to increase their therapeutic efficiencies but not the side effects and complications, to keep the liver function and immunity of patients in a better condition, and to choose the suitable combined therapeutic plan individually. In this paper, the current status of combined interventional therapies for unresectable HCC are reviewed.

COMBINATION OF TACE AND SURGERY

The role of pre- and postoperative transarterial chemoembolization (TACE)

Zhang *et al* suggested that TACE could be performed 2-4 times preoperatively within 6 months according to tumour size, range, location, hepatic function, and TACE effect. It was reported

the 5-year disease-free survival rate was 56.8 % with a mean time of 90.1 months and the 1-, 3- and 5- year survival rates were 79.7 %, 65 % and 56 %, respectively[28,29]. Gerunda *et al* suggested that TACE was able to improve HCC and significantly reduce the incidence of early and overall HCC recurrence and related death after resection[30]. It has been confirmed that pre-operative TACE can necrotize the main lesion and temporarily arrest portal diffusion of neoplastic cells by acting on microvascular infiltration[31]. Nakano *et al* recommended that preoperative TACE should be performed in HCC patients only when LHL15 (the ratio of liver to heart-plus-liver radioactivity of Tc-GSA 15 minutes after injection) was less than 0.91[32]. However, Huang *et al* and Wu *et al* suggested that preoperative TACE for resectable large HCC should be avoided because it could not provide complete necrosis in large tumours and could result in delayed surgery and difficulty in the treatment of recurrent lesions, without any benefit[33,34]. It is concluded that TACE of HCC prior to liver transplantation has no influence on the recurrent rate[35]. However, a more detailed study of this treatment for HCC has not yet been reported. Clavien *et al* demonstrated that cryosurgery after TACE was feasible for cirrhotic livers with HCC and could increase the cure rate of large tumours. TACE might reduce the risk of hemorrhage after cryosurgery, but could also increase the risk of hepatic failure in patients with poor hepatic function. The 5-year survival rate could be raised to 79 %[36].

The results of Lin *et al* indicate that postoperative TACE is useful for prevention and treatment of HCC. It helps improve survival of surgically treated HCC patients[37]. Randomized trials to accurately define the position of this combined technique are needed.

COMBINATION OF TACE AND PEI

Percutaneous ethanol injection (PEI) is widely used with excellent results for small, encapsulated tumours in livers with less than three HCCs[19,38-40]. Ethanol in PEI acts by diffusing within the cells, which causes immediate dehydration of cytoplasmic proteins with consequent coagulation necrosis followed by fibrosis, and by entering the circulation, which induces necrosis of endothelial cells and platelet aggregation with consequent thrombosis of small vessels followed by ischemia of the neoplastic tissues. Advantages for using PEI include[41-43]: no remarkable damage to the remaining parenchyma, relative safety, easy repetition when new lesions appear as in the majority of patients followed for 5 years, application anywhere due to its low cost and easy operation, and fairly good long-term results.

PEI can be carried out either in patients with HCC who have poor hepatic function or in elderly patients (age > or = 70 years)[40,44]. Long-term survival rates of PEI-treated patients are similar to those obtained in matched patients submitted to partial hepatectomy[38, 40, 42]. Livraghi *et al* reported in 746 HCCs with cirrhosis treated by PEI, the 5-year survival rates for single HCC < 5 cm were 47 % for Child A, 29 % for Child B and 0 % for Child C, respectively[45].

PEI has been performed in many hospitals and is now categorized as a potentially curative procedure for patients with HCC. However, the long-term prognosis remains disappointed because of the high recurrent rate among patients with HCC after PEI, especially in those with high levels of alphafetoprotein (AFP) and those without peritumoral capsule or with large lesions and cirrhosis[39,44]. In fact, histological examination of HCC lesions after PEI reveals that viable tissue remains in portions isolated by septa or in extracapsular or intracapsular invasion. It has been demonstrated that the high vascularity of HCC promotes an early wash-out of injected ethanol, so that PEI for patients with hypervascular tumours may be less effective than for patients with hypovascular tumours[46,47].

Combined TACE and PEI is a therapeutic option that has been recently proposed to overcome the weakness of each of the two procedures in the treatment of large HCC[48-50]. The rationale for combination of the two treatments relies on the fact that after TACE tumour consistency is markedly decreased and intratumoral septa are usually disrupted, as a result of the necrotic phenomena induced by the procedure. These histopathologic changes make subsequent treatment with PEI easier, as they provide enhanced ethanol diffusion within the tumour. Consequently, higher doses of ethanol than those used in conventional PEI can be injected, enabling complete and homogeneous perfusion even of large lesions. Moreover, treatment with PEI is facilitated by the TACE-derived fibrous wall around the lesion, which favours a better retention of the injected ethanol within the tumour[46,50,51]. The 5-year survival rate was 50 % in the TACE/PEI group and was 22 % in the TACE group[52]. A favourable outcome of this combined therapy can be expected in patients with solitary and encapsulated HCC (low Okuda stage, AFP level <100 ng/ml), compensatory cirrhosis, and absence of portal vein thrombosis[42,49,51,53].

COMBINATION OF TACE AND RFA

Radiofrequency thermal ablation (RFA) is a minimally invasive and safe technique for the nonsurgical treatment of HCC. Similar to other ablation techniques, the treatment strategy depends on several factors, such as the patient' s clinical status, the stage of liver cirrhosis and of HCC. RFA can be performed percutaneously, laparoscopically or after laparotomy[54]. RFA achieves complete tumour necrosis for small HCC (< or = 3.5 cm in diameter) with fewer treatment sessions compared with PEI, and can also create large volumes of tumour necrosis in a shorter period of time than either laser or microwave therapy. Curley and Izzo suggested that RFA could be performed for unresectable hepatic malignancies less than 6.0 cm in diameter[55]. In addition, equipments used for RFA were less expensive than either laser or microwave equipments[56]. RFA provides local control of advanced liver tumours with low recurrence and acceptable morbidity[57-62]. However, the complication rate is higher with RFA than with PEI[20].

The combination of TACE and RFA induces larger coagulation necrosis areas than RFA without any possibility of revascularization[63-66]. RFA performed after TACE effectively treats HCC larger than those suitable for segmental TACE or RFA application alone[63]. Bloomston *et al* reported that one-year survival was greater in patients undergoing TACE and RFA than TACE alone (100 % *vs* 67 %, P=0.04). Mean survival was longer after TACE with RFA compared with TACE alone (25.3 months +/- 15.9 *vs*. 11.4 months +/- 7.3, P<0.05). No patients suffered significant complications in that study[66]. For multifocal recurrence, RFA can be useful as a complementary technique for lesions not completely treated by TACE[67].

COMBINATION OF TACE AND MCT

It is well known that percutaneous microwave coagulation therapy (MCT) under local anesthesia is a palliative and effective therapy when carried out on a single occasion to treat HCC located near the liver surface, and it can be safely performed under direct visual guidance[21]. MCT may be superior to PEI for the local control of moderately or poorly differentiated small HCC[22, 23]. MCT is also superior to PEI for treating patients with HCC < or = 15 mm in diameter. In such patients with well-differentiated HCC, PEI is as effective

as MCT[68].

The combined therapy of MCT applied within 1-2 days of TACE can effectively treat HCC >2.0 cm but <3.0 cm in dimension. A few microwave electrode insertions and microwave irradiations are needed[69]. Ishikawa *et al* suggested that MCT destroyed the peripheral part of the tumour that might remain viable after TAE, but combination therapy with transarterial embolization (TAE) was preferable, especially when a viable part existed within tumours[70]. However, larger scale clinical trials are required to define the role of this combined therapy in the strategy of oncology.

COMBINATION OF TACE AND LITT

Patients with larger and more than two HCC nodules have a relatively high incidence of recurrence of HCC in the remnant liver, even when coagulation by PEI, MCT or RFA is complete[71-73].

Laser-induced thermotherapy (LITT) is another minimally invasive and attractive method for destroying relatively larger tumours within solid organs by causing carbonization and vaporization in tissue[24,72-75]. MR-guided LITT is a local effective therapy with low morbidity for malignant liver tumours with a maximum quantity of 5 and a size of < or = 5 cm[24,25]. LITT may be also equivalent to limited hepatic resection and may influence long-term survival, achieving results comparable to those of segmentectomies, but local recurrence can occur even in small HCC, while this drawback is infrequent[26].

The rationale for combination of TACE and LITT is based on the fact that LITT can reduce the volume of viable tissue and improve the lesion within the range of TACE effectiveness. Moreover, in the case of multiple lesions in the same patient, it is possible to treat the small lesions with LITT alone and to reduce the number of hepatic segments requiring TACE[74]. Pacella *et al* achieved complete response with a single segmental TACE session in 21 (70 %) of the 30 patients and reported that the 1-, 2-, and 3-year local recurrent rate was 7 % in large HCC, respectively. Complete tumour necrosis was achieved in all 15 (100 %) small HCCs. The 1-, 2-, and 3-year cumulative survival rates were 92 %, 68 %, and 40 %, respectively. The mean number of sessions needed to control large HCC was 4.2[74]. LITT seems to be more beneficial and advisable in combination with TACE for treating patients with relatively larger and multiple HCCs.

COMBINATION OF TACE AND RADIATION

A number of studies have shown the experimental and clinical therapeutic effectiveness of combination of external/interstitial radiation and TACE[76-82]. Delivering the highest irradiation dose within the tolerance of the liver is the key to improve the long-term effect.

Intra-arterial injection of radioactive lipiodol has shown promising results in patients with HCC and portal obstruction. Raoul *et al*. reported that overall survival rates at 6 months, 1, 2, 3, and 4 years were 69 %, 38 %, 22 %, 14 % and 10 %, in the ^{131}I-labeled lipiodol group and 66 %, 42 %, 22 %, 3 %, and 0 % in the chemoembolization group, respectively. In terms of patient survival and tumor response, radioactive ^{131}I-labeled lipiodol and chemoembolization were equally effective in the treatment of HCC, but tolerance to ^{131}I-labeled lipiodol was significantly better[83].

Guo *et al* and Tazawa *et al* regarded the combination of TACE and radiotherapy as an alternative and permissible treatment for large unresectable HCC, and it might be useful to reverse portal vein tumor thrombi in patients with good hepatic function reserve[79, 80]. It was reported the cumulative survival rates of 1, 3 and 5 years were 59.4 %, 28.4 % and 15. 8 %, respectively[80]. Cheng *et al* demonstrated that this combined therapy was associated with better control of HCC than radiation given alone, probably due to the selection of patients with favorable prognosis for the combined treatment[82]. However, it has been reported that the survival of patients with combined TACE and radiotherapy was similar to that with TACE as the only treatment, while a significant portion of the patients treated with radiotherapy developed extrahepatic metastasis[81]. In another study, Yasuda *et al* also confirmed that radiotherapy combined with TAE and PEI did not clearly show improvement of the survival. However, it could effectively control large HCC with minimal toxicity[84].

Whether this therapeutic method can really increase the survival rate of patients suffering from liver cancer, should be determined by further prospective and comparative studies.

COMBINATION OF TACE AND IMMUNOTHERAPY

In the past few years, combined targeting locoregional immunochemotherapy has been reported with encouraging results[85, 86].

OK-432, a biological response modifier (BRM) derived from the weakly virulent Su strain of *Streptococcus pyogenes*, has been applied in combination with locoregional chemotherapy or transarterial embolization for treating HCC in clinic. OK-432 can augment the anti-tumour effect of anticancer agents (cisplatin/mitomycin), because OK-432 itself has a direct cytotoxic and cytostatic activity against tumour cells and inhibits DNA and RNA synthesis in tumour cells. Chemotherapy can also increase the susceptibility of tumour cells to cytotoxic effector cells including lymphocytes, macrophages and neutrophils activated by OK-432 through direct damage or modulation of surface antigens by chemotherapy[87]. In addition, anticancer agents can eliminate the suppressor cells or suppressor factors in the blood or effusion, resulting in augmented anticancer activity of OK-432-activated immunopotentiating cells, especially T-cells[88, 89].

Based on the results of histologic examination in Japan, transarterial immunoembolization (TIE) seems to be more effective than conventional TAE against extracapsular invasion and intrahepatic metastasis in clinic. Data on disease-free survival and recurrence site suggest TIE may be a useful preoperative treatment[90,91]. Such combined transarterial immuno-chemoembolization merits further clinical investigation in patients with unresectable HCC and immunoincompetence.

Other BRMs such as tumor necrosis factor (TNF), cytotoxic T lymphocyte (CTL), tumor infiltrating lymphocyte (TIL) have not been used in TACE in clinic up to now.

COMBINATION OF TACE AND GENE THERAPY

Gene therapy is one of the more promising approaches for patients with advanced liver tumour. Experimental and clinical studies have been reported using cytokine genes (tumor necrosis factor, interleukin-2, interferon), suicide and p53 genes, retrovirus, adenovirus and Epstein-barr virus as vector, AFP enhancer, intraarterial administration, etc.[92-99].

Adenovirus-mediated gene therapy of experimental HCC is hindered by its low transduction efficacy *in vivo*[92]. Gene therapy for cancer requires efficient, selective gene transfer to cancer cells. The delivery of anticancer agents and iodized oil esters as embolic agents through hepatic artery is known as TACE[93]. Shiba *et al* speculated that genes might be efficiently and selectively transferred for HCC using iodized oil esters because these esters might remain together with a genetic vector within HCC selectively[93]. Clinical trials have begun to evaluate the efficacy of gene transfer of cytotoxic genes to metastatic

colorectal tumors through hepatic artery infusion[92]. The efficiency of trans-arterial gene delivery has also been compared to that of intra-tumoral injection. The results of Seol *et al* indicate that gene expression in patients with liver tumour can be enhanced by trans-arterial delivery of the liposome-DNA complex[94].

Combination of TACE and gene therapy leads to a higher transfer rate and higher concentration of drugs without major side-effects and remains an attractive field for clinical application[92,95,96].

COMBINATION OF TACE AND ANTIANGIOGENESIS THERAPY

Development of tumor angiogenesis-targeting agents is often referred to as a new concept in anticancer therapy, and antiangiogenic agents have the following clinical implications. They may overcome drug resistance in solid tumours. Identification of the angiogenic factors in serum or microvessels in tumors can allow the efficacy of the new agents to be quantified. Antiangiogenic agents have low toxicity due to their selective effect on tumour vasculature. Their combination with anticancer agents may potentiate their anticancer effects[100-104]. For the best clinical results, anti-angiogenic therapy should be used in combination with other adjuvant therapies[105-109].

TNP-470 is the first angio-inhibitor which has entered into phase III clinical trial. TNP-470 (AGM-1470) is a fumagillin analogue which inhibits proliferation and migration of endothelial cells and capillary vessel formation at cytostatic but not cytotoxic concentrations. It is believed that ischaemic hypoxia and necrosis induced by TACE stimulate angiogenesis in the residual viable HCC[110]. TNP-470 inhibits the proliferation of new microvascular channels and consequently the development of multiple arterial collaterals[111]. TNP-470 may be particularly effective in inhibiting extrahepatic collaterals and may make it possible to perform TAE repeatedly[112].

Combination treatment of animals showed that TNP-470 potentiated the anticancer effects of some cytotoxic and biological agents[113], but the terminal plasma half-life of TNP-470 was short and the drug was rapidly cleared from the circulation after a single 1-hour infusion[114]. The use of embolic substances (micropheres and medium-chain triglyceride solution), in which TNP-470 is very stable, prolonged retention of the anticancer drug at the tumour site, and augmented the efficacy of anticancer therapy[115]. TAE combined with TNP-470 may enhance the anticancer effect of TAE alone in the treatment of HCC without severe side effects on the liver or body weight gain[116]. This anticancer effect can be enhanced by coadministration of doxorubicin hydrochloride aqueous solution[117].

By combining antiangiogenic agents with TACE used in the treatment of HCC, the limitations of each therapeutic approach will be overcome, leading to enhanced efficacy with diminished toxicity. However, the optimal strategy for the use, monitoring, and validation of antiangiogenic agents in clinic remains unclear.

COMBINATION OF TACE AND TRADITIONAL CHINESE MEDICINAL THERAPY

Traditional Chinese medicinal therapy has gained wide acceptance as a safe, palliative and effective treatment even in patients with large HCC and cirrhosis in China.

Bletilla striata (BS) is a common Chinese medicinal herb and is usually used as an embolic material in TACE for HCC. Its compositions are mucilage, starch, and a little volatile oil[118]. The mechanisms of embolization by BS are attributable to the following factors such as non-absorbent property, mechanical obstruction, effect on coagulative and anticoagulative systems and secondary obstruction due to the injury to wall of blood vessels[119, 120]. Zheng *et al* have confirmed that BS powder has an adherent function and can diffuse slowly in blood flow, leading to mechanical blockade of vessels. The rough surface of BS powder can disintegrate local blood platelets and its mucilage component can make locked erythrocytes agglutinate, thus shortening the clotting time and prothrombin time and causing formation of secondary thrombi[118]. It has also been hypothesized that BS can slowly diffuse into the liver parenchyma around the tumour in colloidal forms, leading to prolonged anticancer effect and inhibition of collateralisation and metastasis of tumour[121]. Compared with gelfoam embolus, BS has the following characteristics. It can produce extensive and permanent vascular embolization, while it cannot be absorbed by body tissue. After embolization, tumour necrosis and shrinkage are significant with less collateral circulation that forms later. The mucilage component of BS is a wide-spectrum anticancer element that may inhibit tumor occurrence and development[118,121]. The 1-, 2- and 3-year survival rates were 44.9 %, 33.6 % and 33.6 % in BS group, and were 48.9 %, 31.1 % and 16.0 % in gelfoam group, suggesting that BS is superior to gelfoam as an embolizing agent, and the transarterial administration of BS may provide a beneficial therapeutic modality for HCC[122].

CONCLUSION

In summary, despite the number of treatment options, HCC usually has a poor prognosis and is one of the malignancies to be cured. The range of treatment options is fairly wide, and the choice is not always easy, given the number of variables to be assessed.

Combined interventional therapies are superior to any single therapy for improving the prognosis and survival of patients with HCC. More multi-center randomized experimental and clinical studies are required to define the indications and role of these combined modalities for treating unresectable HCC.

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