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REVIEW

Loco-regional interventional treatment of hepatocellular carcinoma: techniques, outcomes, and future prospects

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Summary

Loco-regional interventional treatments continue to evolve and to play a major role in the therapeutic management of hepatocellular carcinoma (HCC). Image-guided ablation is established as the treatment of choice for patients with early-stage HCC when transplantation or resection is precluded. Recent refinements in technique have substantially increased the ability of radiofrequency ablation to achieve sustained complete response of target tumors in properly selected patients, and new alternate thermal and nonthermal methods for local tumor treatment are currently under investigation. Transarterial chemoembolization (TACE) is the standard of care for patients with multinodular disease at the intermediate stage. The introduction of drug-eluting beads – that enhance drug delivery to the tumor and reduce systemic exposure – appears to improve anticancer activity and safety profile of TACE compared with conventional regimens. Despite these advances, the long-term outcomes of patients treated with loco-regional therapies remain unsatisfactory because of the high rate of tumor recurrence. The introduction of molecular targeted therapies that inhibit tumor proliferation and angiogenesis has opened new prospects in this regard. Clinical trials focused on combining interventional treatment with systemically active drugs are ongoing. The outcomes of such studies are eagerly awaited, as they have the potential to revolutionize treatment of HCC.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related death [1]. The incidence of HCC is increasing worldwide because of the dissemination of hepatitis B and C virus infection. Surveillance programmes in high-risk patients have led to an increasing number or early diagnoses [2–4]. However, the therapeutic management of HCC has remained a complex issue, as most patients with HCC have underlying liver cirrhosis.

Patients with Child-Pugh A or B cirrhosis, Eastern Cooperative Oncology Group (ECOG) performance status of 0, and solitary tumor or up to 3 nodules smaller than 3 cm in size are classified as early stage by the Barcelona Clinic Liver Cancer (BCLC) staging system [5]. Those with asymptomatic multinodular tumor showing neither vascular invasion nor extrahepatic spread comprise the intermediate stage. Patients who present with cancer-related symptoms and/or with vascular invasion or extrahepatic spread are classified as advanced stage. The terminal stage includes patients who have severe hepatic decompensation (Child-Pugh C) or ECOG performance status greater than 2.

Loco-regional interventional therapies play a major role in the current therapeutic management of HCC.

Image-guided percutaneous ablation is established as the best therapeutic choice for patients with early-stage HCC when surgical resection or liver transplantation are precluded [3,5]. Transarterial chemoembolization (TACE) is the standard of care for patients at the intermediate stage [3,5]. Despite the advances in interventional treatments, long-term outcomes of patients treated with loco-regional therapies remain unsatisfactory because of the high rate of tumor recurrence. The recent addition of molecular targeted drugs – that inhibit tumor proliferation and angiogenesis – to the therapeutic armamentarium has opened new prospects in the treatment of HCC and warrants a sharpened multidisciplinary approach to patient management to optimize treatment options across all stages of the disease. In this article, current and new interventional radiology treatments for HCC are reviewed, and potential synergies between interventional approaches and molecular targeted therapies are discussed.

Image-guided percutaneous ablation

Image-guided percutaneous ablation is currently accepted as the best therapeutic choice for nonsurgical patients with early-stage HCC [3,5]. Over the past two decades, several methods for chemical ablation or thermal tumor destruction through localized heating or freezing have been developed and clinically tested [6,7].

Ethanol injection

The seminal technique used for local ablation of HCC is percutaneous ethanol injection (PEI). Ethanol induces coagulation necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. PEI is a well-established technique for the treatment of nodular-type HCC. HCC nodules have a soft consistency and are surrounded by a firm cirrhotic liver. Consequently, injected ethanol diffuses within them easily and selectively. A series of 4–6 PEI session has been shown to lead to complete response (CR) of about 70% of small lesions [8,9]. PEI has inherent advantages in the cheapness and low morbidity. Its major limitation is the high local recurrence rate, that may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3 cm [10,11]. The injected ethanol does not always accomplish CR because of its inhomogeneous distribution within the lesion – especially in presence of intratumoral septa – and the limited effect on extracapsular cancerous spread. The recent introduction of dedicated multi-pronged PEI needles (QuadraFuse; Rex Medical, Conshohochen, PA, USA) has been shown to overcome some of these limitations, resulting in a rate of sustained CR of 90% in tumors smaller than 3 cm treated with a single-session ablation [12]. An alternate method used for chemical ablation of HCC has been acetic acid injection. However, acetic acid injection has been used by very few investigators worldwide.

Radiofrequency ablation

Radiofrequency (RF) ablation has been the most widely assessed alternative to PEI for local ablation of HCC. Several electrode types are available for clinical RF ablation, including internally cooled electrodes and multitined expandable electrodes with or without perfusion [6]. The thermal damage caused by heating is dependent on both the tissue temperature achieved and the duration of heating. Heating of tissue at 50–55 °C for 4–6 min produces irreversible cellular damage. At temperatures between 60 °C and 100 °C near immediate coagulation of tissue is induced, with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100–110 °C, tissue vaporizes and carbonizes. An important factor that affects the success of RF ablation is the ability to ablate all viable tumor tissue and possibly an adequate tumor-free margin. Ideally, a 360°, 0.5–1-cm-thick ablative margin should be produced around the tumor. This cuff would ensure that microscopic invasions around the periphery of a tumor have been eradicated [6].

Five randomized controlled trials have compared RF ablation versus PEI for the treatment of early-stage HCC (Table 1). These investigations consistently showed that RF ablation has higher anticancer effect than PEI, leading to a better local control of the disease [13–17]. In addition, two recent meta-analyses confirmed that treatment with RF ablation offers a distinct survival benefit compared with PEI, thus establishing RF ablation as the standard percutaneous technique [18,19].

An open question is whether RFA can compete with surgical resection as first-line treatment for patients with small, solitary HCC. A randomized controlled trial (RCT) comparing resection versus ablation in Child A patients with single HCC 5 cm or less in diameter has failed to show statistically significant differences in overall survival and disease-free survival between the two treatment arms [20]. However, neither overall survival nor disease-free survival was primary endpoints for that study. In addition, the sample size was not powered to show noninferiority, and a non-negligible rate of cross-over occurred.

In addition, histologic data from explanted livers in patients who underwent RF ablation as a bridge treatment for transplantation showed that tumor size and presence of large (3 mm or more) abutting vessels significantly affect the outcome of the procedure. In fact, abutting vessels cause heat loss due to perfusion-mediated tissue cooling within the area to be ablated. Complete tumor

Table 1. Randomized controlled trials comparing RF ablation and ethanol injection for the treatment of early-stage HCC.

Author and year	No. patients	Complete response (%)	Local progression (%)	Overall survival (%)	Statistical analysis for survival (*P*-value)
Lencioni, 2003 [13]					
RF ablation	52	91	8	81	>0.05
Ethanol injection	50	82	34	73	
Lin, 2004 [14]					
RF ablation	52	96	17	74	0.014
Ethanol injection	52	88	45	50	
Shiina, 2005 [15]					
RF ablation	118	100	2	80	0.02
Ethanol injection	114	100	11	63	
Lin, 2005 [16]					
RF ablation	62	97	16	74	0.031
Ethanol injection	62	89	42	51	
Brunello, 2008 [17]					
RF ablation	70	96	34	59	>0.05
Ethanol injection	69	66	64	57	

RF, radiofrequency; HCC, hepatocellular carcinoma.

necrosis was pathologically shown in more than 80% of tumors smaller than or equal to 3 cm or in nonperivascular location, but in only 50% or less of those larger than 3 cm or in perivascular location [21]. Another limitation of RF ablation is the applicability of the treatment. Treatment of lesions located along the liver surface, especially in proximity to the gastro-intestinal tract, or adjacent to the porta hepatis or the gallbladder is at risk of major complications [6,7]. It has been estimated that as many as 30% of tumors of small size may not be suitable for RF ablation due to their unfavorable location [22]. Thus, at this point, there is no unequivocal data to back up RFA as a replacement of resection as first-line treatment for patients with early-stage HCC.

New thermal and nonthermal techniques

Several new image-guided ablation techniques are currently undergoing clinical investigation. The thermal and nonthermal methods for local tumor treatment that showed promising initial results include microwave ablation, irreversible electroporation (IRE), and light-activated drug therapy. These techniques promise to overcome some of the limitations of RF ablation in the treatment of HCC. However, further investigation in the setting of randomized controlled trials is required.

Microwave ablation

Microwave ablation is the term used for all electromagnetic methods of inducing tumor destruction by using devices with frequencies greater than or equal to 900 kHz. The passage of microwaves into cells or other materials containing water results in the rotation of individual molecules. This rapid molecular rotation generates and uniformly distributes heat, which is instantaneous and continuous until the radiation is stopped. Microwave irradiation creates an ablation area around the needle in a column or round shape, depending on the type of needle used and the generating power. Only one RCT compared the effectiveness of microwave ablation with that of RF ablation [23]. Although no statistically significant differences were observed with respect to the efficacy of the two procedures, a tendency favoring RF ablation was recognized with respect to local recurrences and complications rates. It has to be pointed out, however, that microwave ablation technology has evolved significantly since the publication of this study. Newer devices seem to overcome the limitation of the small volume of coagulation that was obtained with a single probe insertion in early experiences. An important advantage of microwave ablation over RF ablation is that treatment outcome is not affected by vessels located in the proximity of the tumor.

Irreversible electroporation

Electroporation is a technique that increases cell membrane permeability by changing the transmembrane potential and subsequently disrupting the lipid bilayer integrity to allow transportation of molecules across the cell membrane via nano-size pores. This process – when used in a reversible fashion – has been used in research for drug or macromolecule delivery into cells. IRE is a method to induce irreversible disruption of cell membrane integrity resulting in cell death without the need for additional pharmacological injury [24]. As IRE is a nonthermal technique, issues associated with perfusion-

mediated tissue cooling are not relevant. IRE appears to enable accurate mathematical prediction in treatment planning and to create a sharp demarcation between ablated and nonablated areas. In addition, IRE affects only cell membranes: thus, no other structures (i.e., supportive stroma) are injured, which could greatly improve the clinical application of local ablation. In IRE, general anesthesia with the administration of a neuromuscular blocking agent is mandatory to prevent undesirable muscle contraction. Clinical investigation with IRE has just started and no clinical data are currently available in HCC.

Light-activated drug therapy

Aptocine (Aptocine; Light Sciences Oncology, Bellevue, WA, USA) is a small drug molecule, which is synthesized from a chlorophyll derivative. It has the capacity to concentrate in tumors when administered intravenously. The drug is capable of absorbing long wavelength light resulting in singlet oxygen, which causes apoptotic cell death through oxidation and permanent tumor blood vessel closure. Aptocine is activated by a thin light emitting activator, which is percutaneously inserted intratumorally under imaging guidance. General anesthesia is not required, and lesions abutting vascular structures and located on the liver surface have been safely treated in phase 1/2 studies [25]. Importantly, a secondary tumor-specific immune response due to cytolytic CD8+ T-cell upregulation has been demonstrated in preclinical studies. If confirmed, a tumor directed drug therapy with a systemic effect could have the potential to challenge the existing cytoreduction treatments. Aptocine is currently in a phase 3 clinical trial in HCC.

Transcatheter treatments

Transarterial chemoembolization

Hepatocellular carcinoma exhibits intense neo-angiogenic activity during its progression. The rationale for TACE is that the intra-arterial infusion of a drug such as doxorubicin or cisplatin with a viscous emulsion (e.g., lipiodol), followed by embolization of the blood vessel with gelatine sponge particles or other embolic agents, will result in a strong cytotoxic effect combined with ischemia. Cumulative meta-analysis of all published randomized trials indicates that survival of patients with HCC not suitable for radical therapies treated with TACE is improved compared with best supportive care [26]. However, the outcome of TACE depends on careful patient selection. In a randomized trial that recruited patients with compensated cirrhosis (70% in Child-Pugh A), absence of cancer-related symptoms (81% with ECOG performance status of 0), and large or multinodular HCC with neither vascular invasion nor extrahepatic spread, 2-year survival reached 63%, compared to 27% of the untreated control arm ($P = 0.009$) [27]. In another randomized study, the use of broader enrollment criteria with inclusion of patients with symptoms or limited portal vein invasion resulted in a 2-year survival of 31%. This figure was still superior to one of the untreated control group (2-year survival, 11%); however, no survival benefit was identified in the subgroup analysis restricted to patients presenting with portal vein invasion [28]. As a result of these investigations, TACE has been established as the standard of care for patients with intermediate-stage HCC as defined by the BCLC classification, i.e., asymptomatic multinodular tumor with neither vascular invasion nor extrahepatic spread [4,5].

The ideal TACE scheme should allow maximum and sustained concentration of chemotherapeutic drug within the tumor with minimal systemic exposure combined with tumoral vessel obstruction. The recent introduction of an embolic microsphere composed of a polyvinyl l alcohol macromer (DC Bead, Biocompatibles, Surrey, UK), that has the ability to actively sequester doxorubicin hydrochloride from solution and release it in a controlled and sustained fashion, has been shown to substantially diminish the amount of chemotherapy that reaches the systemic circulation, thus significantly increasing the antitumoral efficacy and reducing drug-related adverse events with respect to conventional regimens [29,30]. In a phase 2 randomized trial, DC Bead-TACE with doxorubicin showed a higher rate of objective response and disease control compared with conventional TACE with doxorubicin, lipiodol and gelatin sponge particles, although the observed difference was not statistically significant [30]. There was also a marked reduction in serious liver toxicity in patients treated with DC Bead-TACE, and the rate of doxorubicin-related side effects was significantly lower in the DC Bead-TACE group compared with the conventional TACE group (12% vs. 26%).

Transarterial radioembolization

The use of external beam radiation therapy in HCC treatment has been limited by the low radiation tolerance of the nontumoral cirrhotic liver. Internal radiation therapy, also called radioembolization, is defined as the infusion of radioactive substances including microspheres containing yttrium-90 (Y90), iodine 131 iodized oil or similar agents into the hepatic artery. Currently, the most popular radioembolization technique consists in delivering implantable microspheres labeled with 90Y, a ß-emitting isotope, into the tumor feeding artery. This allows the delivery of a high radioactive dose to the tumor with reduced toxicity

to the nontumoral parenchyma. Radioembolization has been used in the treatment of HCC not suitable for curative treatment, including patients presenting with portal vein invasion. Data collected in phase 1/2 studies are interesting and may warrant future investigation. No randomized trials are available so far. Clinical research combining the cytotoxic effect of 90Y with the cytostatic mechanism of targeted therapies is currently in progress.

Integrating loco-regional and molecular targeted therapies

Despite the advances in loco-regional treatments, long-term outcomes of patients with early or intermediate-stage HCC remain unsatisfactory because of the high rate of tumor recurrence. After local ablation of early-stage HCC, tumor recurrence rate exceeds 80% at 5 years, similar to postresection figures [31]. Molecular studies have shown that early recurrences – occurring within the first 2 years after curative treatment – are mainly due to the spread of the original tumor, whereas late recurrences are more frequently due to the development of metachronous tumors independent of the previous cancer. On the other hand, in patients with large or multinodular tumor at the intermediate-stage HCC who received TACE, tumor recurrence or progression is almost inevitable, leading to an overall survival rate of less than 30% at 3 years [27,28].

Increased understanding of the molecular signalling pathways involved in HCC has led to the development of molecular targeted therapies aimed at inhibiting tumor cell proliferation and angiogenesis. Sorafenib, a multikinase inhibitor with anti-angiogenic and antiproliferative properties, has been shown to prolong median overall survival and median time to radiological progression compared with placebo in randomized controlled trials and become the current standard of care for patients with advanced-stage tumors not suitable for surgical or loco-regional therapies [32,33]. To date, studies of sorafenib have demonstrated its efficacy in advanced HCC; however, there may also be a role for this agent – or other molecular targeted drugs – in earlier-stage disease, either as adjuvant treatment after curative therapy or in combination with TACE.

Tumor recurrence following TACE is characterised by increased vascular endothelial growth factor (VEGF) production and subsequent angiogenesis. Also, TACE increases VEGF expression in the residual surviving cancerous tissue [34] and induces expression of other pro-angiogenic factors, such as hypoxia-inducible factor 1 alpha (HIF-1alpha) [35]. Based on these findings, combination of TACE with agents with anti-angiogenic properties would appear as a rational approach. A large randomized trial is currently ongoing, comparing DC Bead TACE plus placebo versus DC Bead TACE plus sorafenib. This is the first significant study in which an interventional loco-regional treatment is evaluated in combination with a systemically active molecular targeted drug in HCC. The outcomes of these combination studies are eagerly awaited, as they have the potential to further improve the treatment of HCC.

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