NONSURGICAL TREATMENT FOR LOCALISED HEPATOCELLULAR CARCINOMA

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ABSTRACT

The majority of patients (worldwide) diagnosed with hepatocellular carcinoma (HCC) in 2016 will not be candidates for a potentially curative therapy; however, patients with disease localised to the liver will have options for treatment that are proven to be safe, effective, and worthy of consideration. Transarterial radioembolisation and transarterial chemoembolisation continue to evolve, as does stereotactic external beam radiation therapy with photons or protons. Nonsurgical therapies can provide substantial improvements in quality of life and survival rates compared with best supportive care. This review considers the current use of, and medical evidence for, intra-arterial therapies and external beam radiation options in the nonsurgical management of HCC.

Keywords: Yttrium, selective internal radiation therapy, transarterial chemoembolisation (TACE), transarterial embolisation, external beam radiation therapy (EBRT), proton, stereotactic body radiation therapy (SBRT), radioembolisation, microspheres, gastrointestinal cancer.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 85% of liver cancers worldwide and is the most common malignancy of the hepatobiliary tract. In 2012, 783,000 cases of HCC included 338,000 cases of pancreas adenocarcinoma.[1] HCC is the third leading cause of cancer mortality worldwide. Fewer than 30% of patients with HCC can be approached with curative intent therapies, such as surgical resection, transplantation, or ablation for tumours <3 cm.[1]

This review discusses current treatment options for liver HCC in >70% of patients who are not candidates for curative-intended treatment. Intervention categories include hepatic-arterial therapies, such as radiation implantation and external beam radiation therapy (EBRT). Promising new systemic therapies and immunotherapy agents that may prove helpful in the future are beyond the scope of this discussion.

INTRA-ARTERIAL THERAPIES

The portal venous system supplies ≥75% of the blood flow to normal liver lobules, and the hepatic arteries supply 75–100% of the blood flow to primary or metastatic solid tumours of the liver. Treatment strategies exploiting this vascular anatomy rely on the hepatic arterial flow to deliver chemotherapy, radiation particles (microspheres), or occlusion to cause hypoxic cell death.

Transarterial radioembolisation (TARE) uses inert microspheres (100–800 µm in diameter) released proximally to the HCC tumour; these cause complete obstruction of blood flow to the downstream tissue resulting in cell death in the tumour and normal liver cells where collateral vessels are not close enough for diffusion of oxygen and nutrients. The most common and successful non-radiation approach is transarterial chemoembolisation (TACE) delivery of a cytotoxic agent combined with ischaemia-inducing obstructive particles directly to the tumour. Historically, conventional transarterial chemoembolisation (cTACE) used heterogeneous

particles given in conjunction with multiple chemotherapy agents, with and without lipiodol as the vehicle. TACE using drug-eluting beads (DEB-TACE) purports to use same size microparticles for reproducible saturation and delivery of chemotherapy.

CONVENTIONAL TRANSARTERIAL CHEMOEMBOLISATION

Chemotherapy agents are typically emulsified in lipiodol, an oily contrast agent believed to increase intratumoural retention of a cytotoxic agent. Embolisation of the target vessels is performed via delivery into the hepatic artery of gelfoam, calibrated poly(vinyl alcohol), or acrylic copolymer gelatin particles that cause irreversible occlusion of the feeding vessel. The use of calibrated particles is increasing globally due to the ability to size particles according to target vessel. Vessel occlusion after injection of calibrated particles results in lower peak plasma concentration and increased drug retention within tumours. Therapeutic benefit obtained from adding a cytotoxic agent to bland embolisation was challenged by two clinical trials in the 1990s[2,3] and two meta-analyses,[4,5] both of which suggested that the antitumour effect is mainly driven by ischaemia.

Randomised controlled trials[6,7] in selected patients with preserved liver function have provided data supporting the use of TACE for palliative treatment of unresectable HCC. In a Spanish trial,[6] patients with preserved liver function and no main portal vein thrombosis (PVT) were treated with fixed interval chemoembolisation, embolisation, or best supportive care. The 2-year survival rate after TACE was 63% compared with 27% in untreated patients (p=0.009). A trial in Hong-Kong[7] comprised patients with lobar or branch PVT with preserved liver function and a 2-year survival rate of 31%, again superior to the 11% observed in the control group (p=0.002). Three meta-analyses[4,5,8] confirmed that TACE improves survival of patients and it is now the standard treatment for patients in the intermediate stage of the Barcelona Clinic Liver Cancer (BCLC) staging system (multinodular HCC, relatively preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread).[9]

The range of patients treated by TACE in clinical practice greatly exceeds the margins of the BCLC intermediate stage. As a result, reported survivals are heterogeneous ranging from 53–90% at 1 year, 11–67% at 2 years, and 8–26% at 5 years.[10-18] The median survival average is 16 months, even in the most recent series with unrestricted patient selection.[19-21] Median survival ranges reported by stages are 16–45 months in the early BCLC Stage A, 15.6–18.2 months in intermediate BCLC Stage B, and 6.8–13.6 months in the advanced BCLC Stage C. Prognosis after TACE largely depends on liver function, tumour burden,[10,12,16-18] presence of portal vein invasion, and response to treatment. TACE is contraindicated in patients with PVT as occlusion of arterial blood flow may induce liver failure; however, super-selective TACE may not be harmful in specific patients with segmental branch invasion.

TACE is a safe procedure, although it is frequently followed by side effects such as post-embolisation syndrome, which occurs in >40% of patients and includes nausea, abdominal pain, and fever symptoms that tend to be mild and short-lived. A transient decline in liver function after TACE appears in 20–45% of patients, and acute liver decompensation is reported in 0.1–3% of cases.[22,23] Mortality rates of 0.003–10% in the different series[4,17,18] reflect differences in the target population and TACE regimen. Liver functional reserve is key to an optimal selection and patients should be Child–Pugh Class A or B7 without ascites. A recent consensus from a panel of experts recommends a series of absolute and relative contraindications for the treatment of patients in the intermediate and advanced stages.[24]

TRANSARTERIAL CHEMOEMBOLISATION USING DRUG-ELUTING BEADS

DEB-TACE slowly releases embolising particles, previously loaded with cytotoxic agents, into the tumour. Embolising particles contain a sulfonate-modified poly(vinyl alcohol) hydrogel (DC Beads®, Biocompatibles, Surrey, UK) or a sodium acrylate and vinyl alcohol copolymer (HepaSphere™, BioSphere Medical, Inc., Rockland, MA, USA). Trials investigating embolising particles loaded with doxorubicin show that systemic exposure to this drug is significantly reduced when compared with conventional TACE.[25] In an international randomised trial comparing cTACE with DEB-TACE using DC Beads, the primary endpoints of superiority of DEB-TACE in achieving objective tumour response at 6 months and producing fewer treatment-related serious adverse events in the first 30 days were not met.[26] Tumour response rates were 52% and 44% and time-to-progression was 7.1 months

and 6.4 months for DEB-TACE and cTACE, respectively. A similar 6-month response rate of 51% was reported for HepaSphere Microspheres in a multicentre study.[27] A prospective randomised comparison of DEB-TACE and bland embolisation using the same unloaded particles showed that despite producing a significantly better response rate at 9 months (55% versus 31%), 12-month survival was similar (85.3% versus 86%).[28] Although DEB-TACE does not improve survival over cTACE, DEB-TACE provides a way to perform TACE in a standardised way, and when optimal patients are selected, the beneficial effect of TACE can challenge that of percutaneous ablation. Recent reports from two centres, comprising 300 patients in the early and intermediate stages, show 3-year and 5-year survival rates of 62–66% and 22–38%, respectively.[29] Major complications, including liver abscess, cholecystitis, and pleural effusion, occurred in 4.1% of patients in the Greek series;[28] in the Spanish series,[25] 1.6% of patients had liver failure; the death rate was 10%, of which 0.96% of cases were attributed to treatment.

TRANSARTERIAL RADIOEMBOLISATION

During TARE treatment, radioactive microspheres are injected intra-arterially for internal radiation treatment.[30] Two types of microspheres are available: radioactive glass microspheres (TheraSphere®; MDS Nordion, Ontario, Canada) and resin (SIR-Spheres®; Sirtex Medical Limited, Sydney, Australia). Both types use ^{90}Yttrium as the radiation-emitting isotope. Due to the small diameters of 25–45 μm, radioactive microspheres produce no significant ischaemic effect unlike the >100 μm particles used in TACE. Patients are candidates for TARE if their liver function is preserved (serum total bilirubin <2 mg/dL) and there is no ascites or hepatic encephalopathy present.[30,31]

Clinical trials comparing TARE with other therapies with a sufficient number of patients to answer the question of superiority have not been performed; however, Level II evidence is available from cohort series published in the last 5 years.[32-37] TARE has been used to treat unresectable patients who are not candidates for TACE (advanced stage due to symptoms, PVT, or intermediate stage with very large tumours or extensive bilobar involvement).[38] A case-controlled study with poor TACE candidates indicated that TARE might improve survival compared with experimental therapies or best supportive care (16 months versus 8 months, $p<0.05$).[32] Intermediate stage patients analysed by tumour stage and treated by TARE reached a median survival of 16–18 months[35,37,39] compared with median survival achieved by TACE. Broadly equivalent survivals are also reported in retrospective analyses of single institutions. The remaining treatment options for patients in the intermediate stage who fail to respond to TACE include the antiangiogenic and antiproliferative targeted agent sorafenib or TARE.

Sorafenib is the mainstay for treating advanced HCC; for example, cases exhibiting vascular invasion, extrahepatic disease, or deteriorated performance status patients with at least partially preserved liver function. TARE has no macroembolic effect[40] and can be applied safely to patients with PVT, which offers a median survival of 6–13 months, similar to 6.5–10.7 months reported in the Phase III clinical trials of sorafenib in the same group of patients. In patients with only branch or segmental PVT, survival extends from 10 to 14 months.[34,35,38,41] Due to this growing body of Level II evidence, TARE is now included in the guidelines adopted by the European Society for Medical Oncology (ESMO), the European Society of Digestive Oncology (ESDO), and the National Comprehensive Cancer Network (NCCN).

TARE is used to reduce tumour size to within acceptable limits for liver transplantation, to render non-operable patients operable, or to simplify surgery. Downsizing from UNOS (United Network for Organ Sharing) T3 to T2 was achieved more often with TARE than with TACE (58% versus 31%, $p=0.023$).[42] Atrophy of the radiated lobe after TARE and contralateral lobe hypertrophy resulting from injection of high activity of ^{90}Yttrium in a lobar hepatic artery may be valuable and contribute to resectability.[43] In a group of 21 UNOS T3 stage patients, 29% were downstaged and underwent surgical resection or liver transplantation, with a 3-year survival rate of 75%,[44] comparable with the survival rates in patients with early-stage disease who are treated radically at the time of diagnosis.

Rare complications after TARE resulting from the irradiation of non-tumoural tissues include pneumonitis, cholecystitis, gastrointestinal ulcerations, and liver damage. Liver toxicity is the most challenging adverse event in HCC patients as the majority of these tumours arise in cirrhotic livers, with some degree of reduced functional reserve. A variable incidence of liver

decompensation including ascites (0–18%) or encephalopathy (0–4%) has been reported.[36,37] The incidence of radioembolisation-induced liver disease, characterised by jaundice and ascites appearing 4–8 weeks after TARE in cirrhotic patients, was 9.3% in the largest series reported.[45]

Combinations with Systemic Agents

Clinical trials of sorafenib with intra-arterial therapies are disappointing. Time-to-progression among patients with >25% tumour necrosis or shrinkage at 1–3 months following one or two TACE sessions where participants received sorafenib, was not better than time-to-progression of patients receiving placebo (5.4 months versus 3.7 months, respectively, p=0.25).[46] When continuous sorafenib or placebo was given concurrently with DEB-TACE, safety was not an issue[47] and the hazard ratio for time-to-progression was 0.797 in favour of sorafenib (95% confidence interval: 0.588–1.080, p=0.072). Overall survival was comparable.[48,49] The addition of TARE to sorafenib for intermediate and advanced stage patients is currently being studied in the randomised controlled SORAMIC trial (NTC01126645). An interim analysis of the first 40 patients randomised to radioembolisation with ^{90}yttrium resin microspheres followed by sorafenib (n=20) or sorafenib only (n=20) in this study showed that there were no significant differences in adverse events or Grade 3/4 toxicities between the combination and control arms. A Phase II study comparing DEB-TACE plus sorafenib with DEB-TACE plus placebo has not reached the median overall survival, but the time-to-progression is not statistically different between the two arms.[51] Two retrospective studies and one prospective study suggest that sorafenib with TACE is safe, with varying evidence of an advantage in time-to-progression when used in combination.[52-54]

EXTERNAL BEAM RADIATION THERAPY

Radiation therapy (RT) to liver tumours is limited by the relative radiosensitivity of the sinusoid endothelium, compared with the significantly higher doses of radiation required to confidently destroy HCC cells.[55] Normal tissue complication probability (NTCP) models are based on observed complications after radiotherapy in a specific organ, with known daily and total dose data and specific clinical outcomes measured.[56,57] The accepted endpoint in hepatic NTCP models is radiation induced liver disease (RILD), classically reported in terms of TD5/5 and TD50/5; the total dose of photon radiation, typically to the whole liver, creates a 5% rate of RILD by 5 years post-radiation, and a 50% rate respectively.[56-58]

External Beam Radiation Therapy for Hepatocellular Carcinoma

Three dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) have been mainstays of advanced treatment delivery using computed tomography based datasets to target tumours while sparing normal surrounding tissues. Stereotactic body radiotherapy (SBRT) is a specialised form of 3DCRT that delivers very high single fractions of daily radiation; up to five in total. There are many challenges with EBRT for HCC; however, there has been success using image-guided radiation therapy to assist in delivery of 3DCRT, IMRT, and SBRT, along with respiratory motion compensation and tumour visualisation. Proton beam radiation therapy (PBRT) utilises a different type of energy to photon-based radiation, and represents a treatment that has the physical characteristics to provide superior dose deposition compared with 3DCRT.

Indications for External Beam Radiation Therapy in Hepatocellular Carcinoma

RT has a well-proven ability to sterilise tumours similarly to other local ablative approaches such as radiofrequency ablation.[59] In the BCLC classification, Stage 0 and early Stage A patients who cannot undergo surgical resection, transplant, or radiofrequency ablation, are candidates for RT. In Stages B and C, RT has efficacy in situations where TACE has been ineffective or is unsuitable, such as in patients with portal vein invasion where TACE is contraindicated and TARE may be impossible or ineffective.[59]

STEREOTACTIC BODY RADIATION THERAPY FOR HEPATOCELLULAR CARCINOMA

SBRT for HCC offers an increased ability to spare normal liver tissue from receiving tolerance doses of radiation. Four prospective studies and four retrospective single institution reports have been reported in the literature (2006–2011) with cohort sizes ranging from 8–60 patients. Despite the lack of larger, randomised controlled data, the positive outcomes in all stages of HCC are proven with a wide array of fraction sizes and total doses. Excluding the eight-patient

study, the remaining three studies used at least five different fractionation schedules adjusted for Child–Pugh A or B. One-year survival ranged from 48–79% in the heterogeneous groups.[60-62]

PROTON BEAM RADIATION THERAPY FOR HEPATOCELLULAR CARCINOMA

PBRT offers increased control of radiation dose deposition at any depth in the body.[63] Prospective studies are positive regarding toxicity and tumour control with encouraging overall survival in selected HCC patient groups in Eastern and Western populations.[63] There are 10 prospective studies which have analysed PBRT. Each study reports on greater numbers of patients than those which have looked at SBRT (76-318).[64-67] The outcomes of superiority of SBRT or PBRT in HCC patients are unknown; however, it is likely that SBRT and PBRT will be complementary to each other based on factors such as tumour size, distribution, and location in the liver. Dawson[63] suggested that photon beams (3DCRT, IMRT, SBRT) are best employed in Child–Pugh Class A patients with tumours of <6 cm in size, in the right lobe, near the dome. Protons may be utilised best in Child–Pugh Class B, tumours that are >8 cm, and those that are central and/or medial in the liver.[59] Only Level IIa evidence supports any form of radiation in HCC; however, combined with the retrospective reports of hundreds of patients, there is significant evidence supporting radiotherapy in all stages of HCC.[59]

CONCLUSIONS

HCC patients unable to receive curative approaches can derive significant benefit in quality of life and survival if eligible for the intra-arterial or external therapies presented. New technologies exploiting both approaches are currently in clinical testing, and include external radiation using carbon ion beams, combined chemotherapy, TARE, and variations on TACE both mechanically and via the chemotherapy agent deployed.

TACE is a heterogeneous group of procedures in terms of materials, extent and selectivity of vessel occlusion, and timing of repeated sessions. Good tumour responses are generally observed when a reduced number of smaller tumours are embolised in a selective fashion through a distinct feeding vessel. Two positive clinical trials and three meta-analyses report that TACE is the standard of care for HCC patients in the intermediate stage. DEB-TACE is a more recent standardised way of performing TACE with similar outcomes. Compared with TACE, evidence supporting the use of TARE in the treatment of HCC patients comes from consistent, large cohort series involving patients with more advanced HCC, those unsuitablefor other locoregional therapies, or patients who have failed TACE.

TACE and TARE should be considered complementary tools. TARE can be an alternative to repeated TACE for patients who fail to respond to initial TACE, and as a first option in those patients who are poor candidates for TACE. Results of ongoing clinical trials will soon establish if sorafenib or other targeted therapies improve the outcome of HCC patients treated by TACE and TARE.

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