Role of Transcatheter Intra-arterial Therapies for Hepatocellular Carcinoma

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Transcatheter intra-arterial therapies play a vital role in treatment of HCC due to the unique tumor vasculature. Evolution of techniques and newer efficacious modalities of tumor destruction have made these techniques popular. Various types of intra-arterial therapeutic options are currently available. These constitute: bland embolization, trans-arterial chemotherapy, trans-arterial chemo embolization with or without drug-eluting beads and trans-arterial radio embolization, which are elaborated in this review. (J Clin Exp Hepatol 2014;4:S112–S121)

Transcatheter intra-arterial therapies are widely used loco-regional palliative therapies for the management of intermediate and relatively advanced stage of hepatocellular carcinoma (HCC).[1–4] This is largely so because, the majority of the patients present with advanced disease at the outset and this precludes the use of curative treatment options.[5]

The current article expands on the consensus guidelines discussed and drafted at the INASL task force on hepatocellular carcinoma convened at Puri from February 7,8 2013. Last decade has witnessed important developments in practised intra-arterial therapies. These constitute-bland embolization, trans-arterial chemotherapy, trans-arterial chemoembolization with or without drug-eluting beads and trans-arterial radioembolization.[6] All these types of intra-arterial options have a common goal of producing local tumor destruction but the mechanism of achieving this goal varies.

RATIONALE OF TRANSCATHETER INTRA-ARTERIAL THERAPIES

The liver has a dual blood supply. The dominant supply (about 75%–80%) is from the portal vein while the remaining 20%–25% is supplied by the hepatic artery. During carcinogenesis, HCC becomes increasingly "arterialized" and the hepatic artery becomes its sole supplier resulting in neo-angiogenesis.[7] This fact is utilized by the different intra-arterial therapies for administering cytotoxic drugs/embolizing agents to the tumor through its feeding hepatic artery leading to local tumor destruction and sparing the normal liver parenchyma.

TRANS-ARTERIAL EMBOLIZATION [BLAND EMBOLIZATION, (TAE)]

Trans-arterial embolization was introduced in the 1950s.[7] Embolization can be categorized into bland embolization (TAE), trans-arterial chemoembolization (TACE) and trans-arterial radiotherapy (TART). TAE produces terminal arterial blockade resulting in ischemia and cytotoxic damage to the tumor. TACE refers to a combination of the delivery of chemotherapy followed by embolization of the feeding arterial supply producing twin advantages of action. TART uses internal radiation for destroying the tumor(s) followed by concomitant embolization of the feeding artery.[8]

Embolization aims at occluding the arterial supply of the malignant liver tumor using embolizing agents producing tumor hypoxia and resultant tumor necrosis. Two types of embolizing agents are in use-temporary embolizing agents like gelatin sponge (available as particles, cubes, pellets or powder form), autologous blood clot and degradable starch microspheres, and the permanent or semi-permanent types like polyvinyl alcohol (PVA particles) and steel coils.[9] Gelatin sponge is the most commonly used temporary embolizing material, which is 1–2 mm in diameter. Recanalization of the embolized artery generally takes place within 2 weeks.[10,11] PVA particles produce distal arterial obstruction due to their smaller size and cause semi permanent/permanent occlusion. Hence, in HCC they are mainly used as a second line agent for embolizing the collaterals formed as a consequence to

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Abbreviations: AFP: alpha feto protein; CR: complete response; HAIC: hepatic artery infusion chemotherapy; HCC: hepatocellular carcinoma; LA: laser ablation; OLT: orthotopic liver transplant; PD: progressive disease; PEI: percutaneous ethanol injection; PR: partial response; PVT: portal vein thrombosis; RFA: ablation; SD: stable disease; TACE: trans-arterial chemoembolization; TAE: Trans-arterial embolization; TART: trans-arterial radiotherapy
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repeated embolization with other agents. No consensus exists on the most effective embolizing agent.

TAE has been previously used as an effective treatment for unresectable HCC. The survival benefit[12] and marked anti tumoral effect[13–15] on patients of unresectable HCC have been reported in many studies. A recent study showed a median survival of 21 months with the 1-, 2- and 3-year survival rates of 66%, 46% and 33% respectively.[12]

On comparing outcomes of TAE with TACE, a large meta-analysis (3 RCTs, 412 patients) demonstrated no survival difference between the two techniques[9] However, another study found that compared to TAE, TACE significantly prolonged progression free survival and time to progression, but not the overall survival.[16] Thus, though TAE is reported as efficacious, the ultimate outcome with TACE is better. Hence TAE is no longer recommended currently in the era when the procedure of TACE is available.

TRANS-ARTERIAL CHEMOEMBOLIZATION (TACE)

TACE is a twin procedure of super-selective trans-arterial delivery of the chemotherapeutic agents through the feeding hepatic artery of the tumor followed by administration of the embolizing agents. (Figure 1) This provides a dual attack on the tumor, firstly by producing cytotoxic damage within the tumor by high concentration of the chemotherapeutic drugs and secondly by additional embolization which prevents the washout of the chemotherapeutic drugs from the tumor causing prolonged retention within the tumor site resulting in ischemic necrosis and enhanced tumor destruction.

A. Indications and Contraindications of TACE

TACE was introduced in the late 1970s and since then this technique has come a long way.[17,18] TACE is considered as the primary therapeutic option for unresectable HCC.[5,19] A number of expert guidelines have commented on suitable candidates for TACE.[20–22] The ideal candidates are patients of HCC with multi-nodular tumors with preserved liver function (Child-Pugh class A or B), without vascular invasion or extra-hepatic spread.[14,23] These have been staged as BCLC B and C (with normal main portal vein) based on the Barcelona clinic liver cancer (BCLC) staging.[24]

TACE may also be offered to patients with inoperable small tumors (BCLC stage A), which are not amenable for local ablation due to technical limitations.[25] It is also used as adjuvant therapy or as a means of down-staging the disease before liver transplantation, but whether these approaches provide ultimate survival benefit remains unclear[26–29]

Stringent selection criteria for TACE should be followed for favorable outcomes. Liver functional reserve is a crucial component and patients with Child-Pugh A or B7 without ascites should be encouraged, whilst those with Child-Pugh C status should be excluded since the ischemic insult can lead to severe adverse events.[30] Contraindications of TACE are general contraindications to any intra-arterial procedure, allergic reaction to contrast media, pregnancy, poor liver function, presence of hepatofugal blood flow, main portal vein thrombosis, extra-hepatic metastases, WHO performance status more than 2 and end stage tumoral disease (Okuda III)[10]

Patients with thrombosis of the main portal vein (PVT) are considered a contraindication for TACE. This is due to the risk of aggravating hepatic insufficiency resulting from ischemia causing worst outcomes.[23] However, some contradictory results of survival benefit have been reported[31–34] PVT should therefore not be considered as an absolute contraindication for TACE in patients with preserved liver function.[32,33,35] Better estimates of risk stratification in individual patients are needed.

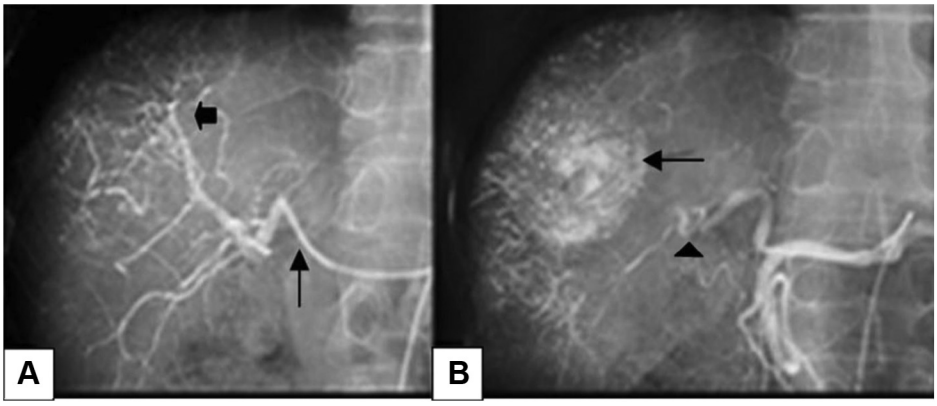

Figure 1 (A) Hepatic angiogram image showing super-selective cannulation of the hepatic artery (arrow) and neovascularity due to supply from the branches of the hepatic artery in the region of the tumor (small arrow) after contrast administration. The chemotherapeutic drug emulsion (doxorubicin 50 mg, cisplatin 100 mg, 10 ml of iodinated non-ionic contrast media and 20 ml of lipiodol) was injected followed by embolization of the feeding hepatic artery using gelatin sponge pledgets B) Post-TACE angiogram image depicting retained lipiodol in the tumor (black arrow) with embolized feeding artery (arrow head).

No standardized protocol exists with regard to the choice of chemotherapeutic agent, dosage, dilution and the rate of injection.[36] Doxorubicin, mitomycin and cisplatin are the common chemotherapeutic drugs used alone or in combination. Irrespective of the choice of the chemotherapeutic drug used, an emulsion of the drug is prepared with an iodized oil called lipiodol, which acts as a carrier and increases the intratumoral retention of the drugs causing a prolonged effect.[37,38]

Use of single or multiple chemotherapeutic drugs have been undertaken in the procedure of TACE.[39,40] A recent three arm randomized trial has shown better response with less number of treatment sessions with the use of multiple drugs in TACE and with drug eluding beads as compared to TACE undertaken with a single drug.[41]

No standard embolizing agent, quantity or guidelines for re-treatment strategy have been recommended for TACE. More intense regimes of repeating TACE every 2 months has been shown to induce liver failure in high proportion of cases.[27]

A number of factors have been correlated with effective post TACE response viz; tumor diameter less than 5 cm, less than 50% replacement of liver by tumor tissue and unilobar tumor. Other prognostic factors include the alpha feto protein [AFP] level, differentiation of HCC, number of tumor nodules, portal vein thrombosis, presence of tumor capsule, and degree of lipiodol retention post-procedure.[14,16,17,21,31,42] Large tumors with poor baseline liver function, have shown least benefit from TACE.

B. Role of TACE as a Combination Treatment

TACE has been successfully used in combination with various modalities for the treatment of relatively large tumors depicting better survival rates.[43–46]

Commonly tried combination modalities with improved results are, percutaneous ethanol injection (PEI), percutaneous acetic acid injection, radiofrequency ablation (RFA), laser ablation (LA), oral chemotherapy and targeted therapy.[47–52]

Repeated sessions of TACE can be used for downsizing the tumor and subsequently making the patient suitable for ablation. Complete response has been achieved in 90% of the large tumors subjected to repeated sessions of TACE followed by LA.[53,54] Similar superior results have been achieved with combination with PEI, and RFA.[55] Better quality of life scores have also been shown in patients treated with TACE with RFA than those treated with TACE alone.[56] Combination of TACE and oral chemotherapeutic drug, sorafenib too is being tried with promising results.[57]

C. Role of TACE as an Adjuvant Therapy

TACE has multiple roles as a palliative treatment. TACE when performed prior to hepatic resection in patients with large tumors, produces reduction in tumor volume. It is safe, efficacious with high rates of pathological response.[23] It destroys remnant cancer cells, decreases recurrence rate and prolongs survival.[9,24] On the contrary, decreasing survival rates have also been reported, possibly due to hepatic and immunological damage occurring with TACE.[25] Role of TACE as an adjuvant therapy thus remains quite controversial. TACE has also been used as adjuvant therapy for preventing postoperative recurrence. Cases where intrahepatic recurrence occurs following resection, TACE is successfully used as a palliative therapy.

TACE also has a role to play in HCC patients planned for orthotopic liver transplant (OLT). It provides a dual benefit - controlling tumor growth as well as producing tumor necrosis. This results in reduced chances of tumor dissemination during surgery. Moreover, down staging of the disease can be achieved making these patients suitable for OLT. TACE is thus the commonly used bridging modality in transplant patients. However, despite achieving tumor down staging, no significant advantage in survival and recurrence rate has been shown in the patients following OLT.[26]

D. Criteria for Successful and Failed TACE

Criteria for the success and failure of TACE relate to the technique and outcome of the procedure. Additionally superselective TACE with an attempt to deliver the drug very close to the tumor has a better outcome than whole-liver or lobar TACE. This minimizes embolization of non-targeted normal liver parenchyma.[9,58] Superselective cannulation of the extra hepatic arterial feeders is even further difficult to negotiate because of the unusually long, tortuous and narrow caliber. Moreover, prolonged repeated attempts at cannulation may lead to spasm of the artery resulting in the procedure being futile.

Detailed assessment of the hepatic arterial anatomy on cross-sectional imaging (mutiphasic CT or MRI) is important. Presence of arterial anomalies, focal narrowing of the feeding artery at the origin or during its course, extreme tortuosity of the artery, narrow caliber, presence of multiple feeding arteries to the tumor can be picked up on imaging and such patients are poor candidates for the procedure of TACE.

Extra hepatic arterial supply is frequently observed in patients with large tumors near the liver surface or with an exophytic component or in contact with bare area of the liver or large tumors with direct invasion into the adjacent organs or extra capsular infiltration.[59–64] Arterio-portal or arterio-venous shunting makes the procedure very difficult and risky. Attempts to block the shunting prior to delivery of chemotherapeutic drugs is important in order to prevent systemic dissemination.

Outcome of TACE is gauged by determining the local tumor response on multiphasic CT or MRI performed at

four weeks post TACE. Tumor response assessment was earlier reported on the basis of the WHO criteria,[65] RECIST[66] followed by the EASL criteria.[67] Recently, the modified RECIST (mRECIST)[68] criteria has been recommended. The mRECIST and EASL criteria have shown to have independent correlation with the survival[69,70] Based on these criteria, the local tumor response has been categorized into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).[47] Figure 2 depicts two malignant masses evaluated by CT showing CR in one mass and PR in the other mass subsequent to the treatment of TACE.

In properly selected patients, TACE is a relatively safe procedure with few minor complications, Post-embolization syndrome is the most frequently encountered complication seen in about 80–90% of the cases. This syndrome consists of fever, abdominal pain, nausea, vomiting, leukocytosis, and increased liver enzymes. It is self-limiting and treated symptomatically in most patients, but may progress to liver failure in very few. Treatment-induced renal dysfunction is also known.

E. Survival with TACE

Outcome of TACE has been studied extensively. A meta-analysis of nine RCTs have shown improved survival following TACE[15] Significant tumor response is noted in 17%–61.9% cases, and poor complete tumor response 0–4.8% as the tumor cells remain viable following TACE.[71,72] Limited effect of TACE occurs in cases of capsular invasion, extra capsular growth or vascular invasion.

Tumor size more than 5 cm is considered as a negative predictive factor affecting overall survival after TACE.[73] Several RCTs, systematic reviews and meta-analysis have demonstrated a survival benefit post TACE in comparison with supportive care despite tumor size.[14,16–18,25,31,74,75] A survival advantage of 82% and 63% for chemoembolization has been shown in comparison to 63% and 27% for supportive care (P = 0·009) at 1 and 2 years respectively.[17] Marked tumor response, with significant survival benefit in the chemoembolization group has been documented.[31]

The largest cohort study of TACE for unresectable HCC on 8510 patients depicted a median survival of 34 months and a survival benefit at 1, 3, 5 and 7 year as 82%, 47%, 26% and 16%, respectively with negligible procedure-related mortality (0.5%).[19] A solitary study from India[76] in which TACE was done for relatively larger tumor size [upto16 cm (Mean size 6.6 ± 3.92 cm], the cumulative survival rate at 1,2,3 years was 66%,47% and 36.4% respectively(Table 1). The degree of liver damage, TNM stage and alpha-fetoprotein values were independent predictors of patient survival.

It is quite evident that the extent of benefit is based on the technique used and the stringent inclusion criteria. A recently published meta-analysis using the Cochrane of large number of studies, has questioned the beneficial role of TACE in treatment of intermediate HCC. Authors evaluated all the randomized trials comparing TACE or TAE versus placebo, sham or no intervention. They excluded the trials with inadequate randomization. Meta-analysis using inverse variance method and subgroup analysis regarding intervention regime, trial truncation or co-interventions was undertaken. The authors concluded that there was lack of firm evidence to either support or refute the procedure of TACE or TAE in patients with unresectable HCC.[77] This generated a lot of controversy. Subsequently, the Society of Interventional Radiology contested this outcome of the Cochrane meta-analysis. They suggested that the conclusion about TACE made by this Cochrane collaboration had lack of validity because two different types of studies were included (TACE and TAE) in the same analysis and secondly there was a

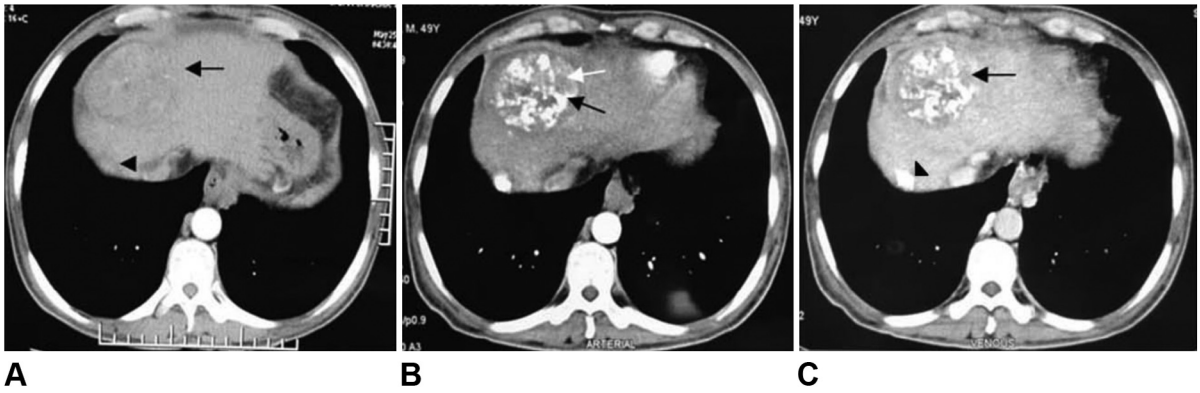

Figure 2 Pre TACE arterial phase CT image of the liver depicting two enhancing tumors, a large tumor in segment 8 (arrow) and a small tumor in segment 7 (arrow head). Patient was then subjected to TACE. Post TACE CT was done at 4 weeks. B) Arterial phase image showing inhomogenous dense lipiodol deposition in segment 8 (black arrow) and small areas of enhancement within the tumor (white arrow) which shows washout in the venous phase [arrow, (C)] suggestive of residual disease. The small segment 7 tumor shows complete coverage with dense lipiodol with no areas of enhancement in arterial and venous phase images B and C (arrow head), suggestive of complete response.

Table 1 Cumulative Survival Following Trans-arterial Chemo-embolization in Advanced Hepatocellular Carcinoma.

Study		Number of patients	Survival (%)	
			1 year	2 years
TACE {Gelfoam powder, doxorubicin [50 mg]}	Pelletier etal[71] (*J Hepatol*, 1990)	21	24	NR
TACE {Gelfoam particles, cisplatin [70 mg]}	Group d'Etude de Traitment du Carcinome He'patocellulare[30] (*N Engl J Med*, 1995)	50	62	38
TACE {Gelfoam, cisplatin [2 mg/kg]}	Pelletier et al[75] (*J Hepatol*, 1998)	37	51	24
TACE {Gelfoam, cisplatin [maximum 30 mg]}	Lo et al[31] (*Hepatology*, 2002)	40	57	31
TACE {Gelfoam, doxorubicin [25–75 mg/m^2]}	Llovet et al[13] (*Lancet*, 2002)	40	82	63
TACE {Lipiodol, anticancer agent, gelatin sponge}	Takayasu et al[19] (*Gastroenterology*, 2006)	8510	82	47 (3 years)
TACE {Lipodol, Mitomycin C 10 mg}	Herber et al[74] (*Rofo*, 2007)	94	71.6	33.9
TACE {doxorubicin 50 mg, cisplatin 100 mg, 10–20 ml of lipiodol, gelfoam}	Paul et al[76] (*Indian J Radiol Imaging*, 2011)	71	60.8	34.4

NR = not reported.

selection bias in the studied included. Bases on these facts, they suggested re-analysis of the data.[78]

TACE is a safe and effective procedure and has become an established palliative therapy for intermediate stage of HCC[20–22]. TACE also has a role to play as an adjunct to surgical resection, bridging therapy before transplantation and as a combination modality used in conjunction with other ablative therapies or oral chemotherapy for treatment of advanced HCC.

TRANS-ARTERIAL CHEMOTHERAPY (TAC)

Trans-arterial chemotherapy (TAC) pertains to intra-arterial infusion of the chemotherapeutic drugs by selective catheterization of the hepatic artery targeting the tumor(s). The rationale for administering intra-arterial regional chemotherapy is to maximize the drug concentrations within the tumor with minimal systemic toxicity and increased local therapeutic response.[79]

TAC has been used in patients with unresectable with or without portal vein thrombosis (PVT).[80] Role of trans-arterial therapies in the treatment of advanced HCC has been fully established. However, there is still controversy as to which therapy is better. Limited evidence comparing the twin techniques of TACE and TAC are available. No difference in survival has been observed between TACE and TAC,[81] however, TAC produces less tumor necrosis than TACE, particularly, in tumors more than 3 cm.[82] Additionally, a meta-analysis has suggested lack of clinical benefit following the procedure of TAC.[83] Hence TAC is not preferred any more.

The chemotherapeutic drugs can also be periodically administered in an infusion through a catheter port directly through the hepatic artery and this technique is called Hepatic artery infusion chemotherapy (HAIC).[84,85] This differs from the procedure of TAC in the sense that no arterial port is left behind and the need for repeating the procedure is assessed on imaging at one month. In HAIC, the arterial port catheter systems are kept for long-term use for delivery of intra-arterial chemotherapy, which historically were placed surgically earlier. However, now, with the advances in the minimally invasive techniques, these ports can be placed percutaneously. This allows easy and repetitive infusion therapy without causing much damage to the vessels and keeps the patient comfortable. HAIC has been primarily used for the treatment of liver metastases[86,87] but has also been employed successfully for treating advanced HCC.[84,85,88,89] Comparison of trans-arterial chemoembolization and infusion chemotherapy for treating unresectable HCC patients has shown no significant difference in the median overall survival time. Further, treatment intensification by adding embolization has not increased survival over chemoinfusion therapy alone.

DRUG-ELUTING BEADS

DEBs are microspheres that can be loaded with chemotherapeutic agents and used for chemoembolization (DEB-TACE). There are several commercially available products, the commonest being PVA microspheres (DC Bead; Biocompatibles, Farnham, UK), which imbibe doxorubicin by immersion, and acrylic copolymer microspheres (SAP Quadrophere [Hepasphere in Europe]; BioSphere Medical, Rockland, MA) are beads that can also imbibe doxorubicin or cisplatin. DEBs produce controlled, sustained release of chemotherapy at decreased peak plasma levels within the systemic circulation.[90] Due to this the systemic toxicity of the chemotherapeutic drugs is much less and moreover the local response rates (tumor response) is better.

A. Drug Eluting Beads Versus TACE

Studies comparing DEB-TACE with conventional TACE (gelfoam-lipiodol particles) are encouraging.[91] In initial

reports in patients with preserved liver function (cirrhosis Child Pugh Class A and B) significantly decreased liver toxicity and lower systemic side effects (such as alopecia and marrow suppression) were observed with comparable local response and survival.[92] Even in patients with more advanced disease (Child-Pugh B, ECOG 1, and bilobar or recurrent disease), a significantly better local response and survival has been noted.[92] Improved local response and fewer treatment sessions have been reported with the use of DEB-TACE in comparison with conventional TACE. Decreased post embolization syndrome with 100–300 μm versus 400–600 μm beads has also been documented.[93] DEB-TACE has been associated with fewer side effects and lower hospitalization rates compared to TACE. However, despite these advantages, no cost benefit has been documented.[94] Since cost and availability is a major concern in the developing world, this procedure is limited to only few centers in India. Further studies are required to demonstrate the cost-effectiveness of DEB-TACE compared to conventional TACE.[95]

TRANS-ARTERIAL RADIOTHERAPY (TART)

Trans-arterial radiotherapy (TART) refers to the percutaneous intra-arterial injection of micron-sized embolic particles loaded with a radioisotope. The intra-arterial radioactive compounds have the ability to deliver high doses of radiation to the small target volumes and produce relatively low toxicity profile.

Internal radiation with Iodine 131, Rhenium or Yttrium 90 glass or resin particles have shown antitumoral effects with a safe profile in the registries.[96]

The therapeutic efficacy of TART essentially depends upon the radiation as opposed to the ischemia associated with chemoembolization or pure embolization. The radio-biological effect results from beta irradiation, which favors destruction of tumor cells surrounding the microvessels containing a high radioactive ligand concentration.

Radioisotopes available for embolization are many. Both ^{131}I-Lipiodol and Yttrium 90 m (^{90}Y) are beta emitters. ^{90}Y has a half-life of 64.2 h and a maximum tissue penetration of 10 mm within the liver. Because of the selective permeation of the tumor vascular plexus, ^{90}Y radioembolization can deliver extremely high levels of radiation (up to 150 Gy), with tolerable exposure to normal parenchyma.[97,98] With radio-iodinated lipiodol (^{131}I-Lipiodol), a proportion of the compound migrates towards the tumor microenvironment through an increased vessel permeability. These radioactive compounds are slowly cleared because of the lack of lymphatic vessels, Kupffer cells, and endocytosis in the tumor tissue.^{131}I–Lipiodol has disadvantages mainly due to the radioprotection constraints, logistics of maintaining inventory.

Hence, both Iodine-131 and Rhenium have become obsolete. Current procedures use ^{90}Y referred to as ^{90}Y selective internal radiation therapy (SIRT). Delivery of ^{90}Y is either bound to resin (SIR-Spheres®, Sirtex Medical, Lane Cove, Australia) or embedded in a glass matrix (TheraSphere®, MDS Nordion, Kanata, ON, Canada). In ^{90}Y microsphere therapy, pre-therapy intra-arterial 99mTc-labeled albumin macroaggregate (MAA) scintigraphy is mandatory to quantify potential liver-lung shunting and to exclude blood reflux to bowel, stomach or pancreas.[99] The main difference between glass spheres and resin spheres is the activity in each sphere, being much higher in the former (about 2500 Bq) at production time compared to about 50 Bq in one resin sphere. Commercially available vials of glass and resin spheres contain up to 20 GBq and 3 GBq respectively. For the same desired activity, glass spheres probably have less embolic effect on micro vessels, being injected in much limited number. Between the SIR spheres and theraspheres, the later have less embolic load and can be tried even in cases with portal vein thrombosis. While the SIR spheres have a shelf life of 24 h, the theraspheres can be used till 15 days.

^{90}Y-microspheres are delivered according to the tumor burden. Hepatic arterial catheterization should be performed. In general, the radiopharmaceutical is delivered at the lobar artery level to be distributed to numerous tumors in that lobe. Sometimes, in cases of lower tumor load, a more selective delivery at the segmental artery level is done. To ensure safe and accurate delivery of 90Y-microspheres, the procedure precludes mandatory evaluation of the shunt fraction and mesenteric vascular anatomy to assess arterial variants and to prevent radiation induced pneumonitis, gastric ulcers, pancreatitis etc. This may exclude a significant number of patients and thus add to the cost.

The side effects include transient fever, fatigue, mild transaminitis, thrombocytopenia with ^{131}I lipiodol, and specifically with ^{90}Y spheres; fatal risk of radiation pneumonitis and radiation induced liver fibrosis can occur.[100]

A. Indications and Contraindications of TART

Many patients of HCC have associated portal vein thrombosis, making them unsuitable for TACE, depending upon the level and severity of thrombosis. Such patients can be offered internal radioisotope therapy to prolong their survival and improve the quality of life.

TART is indicated in patients of unresectable HCC with Child-Pugh A disease, regardless of portal vein thrombosis. In Child-Pugh B and portal vein thrombosis, the outcomes have been poor. However in patients with branch portal vein involvement, it has been considered safe.[101,102]

Absolute contra-indications to TART include: contraindications to gaining trans-arterial access, and pregnancy/lactation. Relative contraindications are advanced child pugh score [> than 7], renal failure, significant extrahepatic disease and previous treatment with external radiation or oral treatment with the

chemotherapeutic drug capebine within 2 months [due to increased risk of radiation induced liver disease]. Specific contraindications for Yttrium spheres are significant artrio-portal shunting, lung shunt fraction >20% [which may cause radiation pneumonitis], significant shunting to other organs like bowel/pancreas [can cause pancreatitis]. Though presence of significant concurrent shunting precludes the use of Yttrium spheres but ^{131}Iodine is not contraindicated though it is not available widely.[103]

Multiple studies have demonstrated radiological and clinical response with ^{90}Y.[104] Patients with Child-Pugh A disease, regardless of portal vein thrombosis, have derived maximum benefit, whereas those with Child-Pugh B and portal vein thrombosis have had poor outcomes.[105] Rhennium too has been shown to be effective, safe and well tolerated in patients with unresectable HCC. However, the availability of Rhennium is a constraint here. A multicentre trial from India depicted survival rates at 6, 9, 12, 24 and 36 months as 100%, 95 5%, 90.5%, 58.5% and 30.5% respectively with a median survival of 980 days.[106] The overall survival rate of 46% and 23% at 1 and 2 years has also been shown by another multicentric study.[107] It has also been tried in patients with post-radiofrequency ablation recurrences as well.[108]

B. TART Versus TACE

Compared with TACE, TART has shown comparable efficacy in terms of local response and time to progression and superiority in terms of downstaging for transplantation.[109] Contradictory outcomes have been reported with TART recently. Retrospective studies comparing TART and TACE have depicted similar efficacy and toxicity[110–112] while certain prospective studies have shown better local response and comparable survival with TART.[96,105]

In conclusion, transcatheter intra-arterial therapies are established effective techniques for the treatment of unresectable HCC. TACE is the established primary palliative therapeutic option for BCLC B, C (normal main portal vein) and in some select cases of BCLC A stage of HCC. The procedures of TAE and TAC have not documented any additional clinical benefit and are no longer practiced these days. DEB-TACE achieves good local response rates and less systemic side effects. Further evidence for long term survival and cost benefit are still emerging. Use of Iodine-131 and Rhenium for the procedure of TART have become obsolete. TART with Yttrium 90 is the current standard and may be preferred in select patients of advanced HCC with portal vein thrombosis having good liver function. These newer techniques of DEB-TACE and TART with Yttrium 90 have no doubt added on to the existing options but have limitations of cost and availability for wider use in the developing world. Choice of the type of intra-arterial therapy should be based on the careful assessment on patient to patient basis and taking into cognizance the important factors like indications, side effects, efficacy, availability, and cost-effectiveness.

CONFLICTS OF INTEREST

All authors have none to declare.

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