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Liver targeted therapies for hepatocellular carcinoma prior to transplant: contemporary management strategies

Mustafa Nazzal[1], **Sameer Gadani**[2], **Abdullah Said**[1], **Mandy Rice**[1], **Obi Okoye**[1], **Ahmad Taha**[1], and **Krista L. Lentine**[1,3]

[1]Division of Abdominal Transplant Surgery, Department of General Surgery, St. Louis University Hospital, USA

[2]Interventional Radiology, Department of Radiology, St. Louis University Hospital, USA

[3]Division of Nephrology, Department of Medicine, St Louis University Hospital, USA

Abstract

Hepatocellular carcinoma (HCC) is an aggressive neoplastic disease that has been rapidly increasing in incidence. It usually occurs in the background of liver disease, and cirrhosis. Definitive therapy requires surgical resection. However, in majority of cases surgical resection is not tolerated, especially in the presence of portal hypertension and cirrhosis. Orthotopic liver transplant (OLT) in well selected candidates has been accepted as a viable option. Due to a relative scarcity of donors compared to the number of listed recipients, long waiting times are anticipated. To prevent patients with HCC from dropping out from the transplant list due to progression of their disease, most centers utilize loco-regional therapies. These loco-regional therapies(LRT) include minimally invasive treatments like percutaneous thermal ablation, trans-arterial chemoembolization, trans-arterial radio-embolization or a combination thereof. The type of therapy or combination used is determined by the size and location of the HCC and Barcelona Clinic Liver Cancer (BCLC) classification. The data regarding the efficacy of LRT in reducing post-transplant recurrence or disease-free survival is limited. This article reviews the available therapies, their strengths, limitations, and current use in the management of patients with hepatocellular carcinoma awaiting transplant.

Keywords

Loco-regional therapy; hepatocellular carcinoma; orthotopic liver transplant

Introduction

Hepatocellular Carcinoma (HCC) is the third most common cause of cancer-related death worldwide [1–3] and if left untreated the prognosis is dismal [2]. The definitive treatment for HCC is surgical resection. However, HCC often occurs in the background of liver disease in 70–90% of cases [4]. In the presence of cirrhosis and portal hypertension, surgical resection

*Correspondence to: Mustafa Nazzal, Division of Abdominal Transplant Surgery, Department of General Surgery, St. Louis University Hospital, 3635 Vista Avenue, St. Louis, MO 63110, USA, Tel:419-508-6361; Fax: 314-577-8837; mustafa.nazzal@health.slu.edu.

has a higher morbidity and mortality rate, and as a result, orthotopic liver transplant (OLT) is the ultimate treatment in patients who are unsuitable for liver resection. Liver transplantation of HCC patient is a relatively recent practice. In fact, in 1989, the U. S. Department of Health and Human Services specifically identified HCC as a contraindication for OLT [5].

Mazzaferro et al. [6] showed that when transplantation was restricted to patients with early HCC within the Milan criteria (MC), which is defined as single lesion less than or equal to five cm or up to three separate lesions, none larger than three cm, a four-year recurrence-free survival rate of 83% could be achieved. Survival in carefully selected patients undergoing OLT for HCC is only slightly worse than survival of patients undergoing OLT for non-malignant causes [7–11]. The Mazzaferro et al. study was later challenged by a study from University of California-San Francisco conducted by Yao et al., which suggested a more liberal criterion for liver transplantation with very comparable outcomes [12].

After the implementation of the Model for End-Stage Liver Disease (MELD) exception points for the HCC liver allocation system in 2003, waitlist times for MC HCC patients were significantly reduced. However, in 2013, a new MELD sharing system was implemented. Consequently, the waiting time for patients with HCC can vary as well as the rate of tumor progression beyond the Milan criteria, leading to a “drop out”, ranging from 30–40% [13].

In an effort to reduce the dropout rate, most liver transplant centers have utilized bridging therapies in the form of liver targeted therapies, such as trans-arterial chemoembolization (TACE), trans-arterial radiotherapy (TARE) or percutaneous ablation (eg microwave, radiofrequency or cryoablation). Interventional radiologists usually perform these procedures. The choice of the therapy depends on the size, number, location of the HCC, BCLC classification and patient's body habitus. Typically, the decision to treat and type of therapy to be used is decided on a case-by-case basis in a multispecialty tumor board.

Heckman et al. [14] demonstrated the safety of LRT but could not find any survival benefits in regard to these different therapies. Stockland et al. [15] reinforced these findings, however he found that the mortality rate was higher in the TACE group due to non-cancer related deaths. Decaens et al. [16] compared TACE patients to matched controls and also found no difference in mortality.

Trans-arterial chemo-embolization “TACE”

Trans-catheter arterial chemoembolization (TACE) is currently the most popular neo-adjuvant treatment option for patients with HCC prior to OLT. It is typically performed in patients with multifocal HCC, single HCC larger than 3 cm or small HCC (< 3 cm) located in the region of the liver not accessible for percutaneous thermal ablation. Conventional TACE (cTACE) is characterized by direct administration of a chemotherapy drug into the liver tumor, usually doxorubicin, mitomycin and/or cisplatin which is mixed with lipiodol as a carrier and an embolization agent followed by bland embolization [17]. This helps in maximizing the concentration of the chemotherapeutic drugs in the tumor for cytotoxicity with minimal systemic concentration and effect. As a result, this technique utilizes embolization as well as chemotherapy to induce ischemia and aid in tumor necrosis

[18].DEB-TACE is the next step in evolution of this technique and involves direct injection of the tumor with embolization beads loaded with doxorubicin [19,20]. DC beads of variable size (70–150 and 100–300 micron) are injected super-selectively into the arteries supplying the tumor. These beads located in and around the tumor, continue to release chemotherapeutic agents over time, thus tumor necrosis is achieved by ischemia induced by the beads and cytotoxicity from the chemotherapy. Newer forms of DEB-TACE treatment utilize beads loaded with idarubicin (diameter 300-500 μm) [21]. TACE is contraindicated in patients with (i) markedly abnormal liver function – high MELD or Child Pugh Score, (ii) extensive vascular disease precluding access to the hepatic artery, (iii) TIPS, or (iv) ascites.

TACE is frequently combined with percutaneous thermal ablation when HCC is larger than 3 cm in size. Typically, TACE is performed first and then followed by thermal ablation. TACE reduces the vascularity of the tumor because of is embolic effect, and therefore creates a ‘heat sink’ effect during thermal ablation. This leads to relatively increased size of the ablation zone during the thermal ablation.

It has been recognized that a six-month waiting period on the transplant list is associated with a 7.2% cumulative dropout probability, and this rate rises to 37.8% and 55.1% at 12 and 18 months, respectively [12]. Thus, utilizing bridging therapy prior to OLT is essential to controlling tumor growth and inducing tumor necrosis to prevent dropout. In addition, pre-transplant bridging therapy can reduce tumor recurrence and improve post-transplant survival. According to the most recent Scientific Registry of Transplant Recipients (SRTR)data, the majority of transplant centers utilize TACE as the standard for bridging therapy [22] despite the lack of conclusive evidence to support this practice. Some studies have shown a decrease in dropout rate after TACE [23-27].Aloia et al. [27] demonstrated that the decrease in the patient dropout rate on the wait-list was statistically significant if the wait-time was between 4 to 9 months. Similarly, a study by Graziadei et al. [24] showed a decrease in dropout rate due to TACE, as well as a survival rate of 94% at five years and tumor recurrence rate of 2%.

Oldhafer et al. [28] showed significant tumor necrosis, greater than 50%, in 66% of patients that received preoperative TACE, but no significant difference in the one and three-year survival rate in the preoperative TACE group compared to the non-TACE group. Furthermore, other studies showed that patients who received a transplant, but were unresponsive to TACE had a much higher rate of tumor recurrence than patients with no tumor progression during the wait.

Decaens et al. [16] performed a study incorporating 479 HCC patients. Both patients and controls were matched for pre-LT tumor characteristics, period of transplantation, time spent on the waiting list, and pre and post transplantation treatments. The study found that TACE had no impact on overall or disease-free survival. Likewise, several studies failed to show that neo-adjuvant TACE would improve survival or decrease tumor recurrence after OLT [28–31]. The pertinent question that needs investigation is whether there is a patient population, tumor characteristic, or time frame for treatment with TACE that might decrease post-OLT tumor recurrence or mortality.

Trans-arterial radio-embolization (TARE)

Of the therapeutic tools discussed in this review, radio-embolization is a more recent addition to the armamentarium of nonsurgical treatment options for intermediate and advanced stage HCC. TARE uses Yttrium-90 (^{90}Y) coated beads to treat HCC. Y90 is a beta-emitting radioisotope, which emits radiation that only travels a small distance (approximately 2.5 mm) within the liver. These particles are deposited in the hepatic arterial system, and lodge in hepatic end-arterioles within the tumor, which is driven by the hypervascular nature of HCC. The arterial flow to a hepatocellular carcinoma is higher than that of normal liver, thus the ^{90}Y particles preferentially flow to tumor [32]. The half-life of ^{90}Y is 2.67 days and within two weeks after treatment, more than 95% of the radiation is delivered to the tumor. TARE is used for palliative treatment of advanced disease which cannot be treated in other ways, for tumor down-staging before liver transplantation, or as an adjuvant therapy for surgically resected HCC. More recently, consideration of ^{90}Y as a first line therapy and/or in addition to Sorafenib has been considered for non-surgical candidates. As stated by Salem et al. [33] there are various considerations in determining eligibility for radio-embolization, which include ECOG performance status, liver function tests, and absence of significant lung shunting or collateral flow to the gastrointestinal tract.

TARE has been shown to limit tumor progression and is currently used as a bridging therapy for HCC prior to liver transplant [34, 35]. Although data about TARE is scarce, studies showed good safety and efficacy [36] with complete tumor necrosis [37]. Some studies have shown TARE-^{90}Y preference over TACE, due to a lower risk of post-embolization syndrome [38], no hospitalization and higher response rates [39]. Moreover, TARE might be more suitable for HCC patients with portal vein thrombosis due to the small size of TARE particles compared to the TACE which tends to induce ischemia and necrosis. Furthermore, given its more durable response in HCC compared to TACE, TARE might be the preferred choice as a bridge to transplantation [39].

Percutaneous ablation

There are various percutaneous thermal and non-thermal ablation techniques available. Frequently used thermal ablation techniques include: radiofrequency ablation (RFA), Microwave ablation (MWA) and Cryoablation. High frequency ultrasound (HIFU) is an experimental thermal ablation technique. Non-thermal ablation techniques are not frequently used clinically. They include irreversible electroporation (IRE), percutaneous ethanol injection and percutaneous laser ablation [40]. Of all the available percutaneous ablation techniques, RFA and MWA are most frequently used with excellent and abundant clinical data available in the literature.

RFA was the first available thermal ablation technique. It is typically used in HCC smaller than 3 cm in size. RFA is a form of thermal ablation which increases local tissue temperature causing coagulative necrosis leading to tissue death. A single electrode is placed within the tumor and more dispersive electrode (grounding pad) is placed on the patient's skin. With the patient being part of the electric circuit, an alternating current is passed between the two electrodes via a radiofrequency generator, resulting in agitation of the tissue ions and

generation of heat. The volume of tissue affected by lethal heat depends on the intrinsic conductivity as well as tissue impedance to the heat and electrical current [41,42].

The efficacy of RFA is limited by the tumor size, with multiple studies demonstrating decreased rate of complete tumor necrosis in medium (3.1 to 5 cm) and large HCC (> 5cm), including only 24% rate of complete tumor necrosis in the latter group according to Livraghi et al [43]. Another limitation of RFA appears to be its susceptibility to the “heat sink effect” (perfusion mediated cooling) in which nearby by vessels (particularly those larger than 3 mm) compromise the system's ability to reach the necessary temperatures to achieve cell necrosis in the tumor areas adjacent to these blood vessels. To mitigate this effect, combination of trans-arterial chemoembolization with drug eluting beads (DEB-TACE) to reduce the tumor perfusion followed by RFA has been used [17,44–46].

There are some studies supporting the fact that RFA can be considered as the treatment of choice for patients with single HCC less than 2 cm even when surgical resection is possible and other treatment can be used as salvage therapy for the few cases in which RFA is unsuccessful or unfeasible [47]. RFA was considered as the second most common LRT prior to LT after TACE [48]. Some studies supporting RFA as an effective bridge to OLT for patients with compensated liver function and safely accessible tumors [49–51]. On the other hand, RFA for tumors greater than 3 cm is suboptimal as incomplete tumor necrosis has been reported as high as 40–70% in explanted livers from patients who underwent OLT [52].

Newer percutaneous ablation therapies look to overcome the limitations of RFA for medium and large size HCC. These include microwave ablation (MWA), which achieves higher temperatures more rapidly, and Irreversible electroporation (IRE), which disrupts the cell membranes. While IRE is still experimental, MWA has been accepted in many clinical practices based on data available in the literature.

MWA utilizes a large gauge antenna to deliver electromagnetic waves much higher in energy than RFA (ranging 900 to 2400 MHz, while radiofrequency is typically around 400 kHz) to thermally ablate the tumor. This results in rotational changes in the polar molecules as they continuously attempt to realign creating frictional heating and ultimately tissue necrosis. MWA ultimately confers several potential advantages, including the ability to penetrate biological tissues with low electrical conductivity or high impedance (i.e. lung and bone) as well as dehydrated tissues. As a result, microwave energy can reach much higher temperatures more expediently improving delivery to a larger surrounding tissue volume. This also makes microwave energy less susceptible to “heat sink effect”. Additionally, the use of multiple antennas can be applied to create a larger ablation zone, potentially making it more advantageous for medium and large HCC [53].

While several studies have compared the local efficacy of RFA and MWA, few studies have compared the long-term outcomes. Early generation microwave systems likely suffered from the relative difficulty of delivering and distributing MW energy, possibly explaining why earlier studies typically favored RFA, such as that by Ohmoto et al. [54]. However, more recent studies have begun to advocate MWA, with improved newer generation systems, as an excellent and equivalent alternative to RFA. A retrospective study by Ding et al. [55]

compared several key safety and efficacy parameters in 98 RFA treated and 131 MWA treated HCC meeting Milan criteria, finding no significant difference in complete tumor necrosis (RFA 99.0% *vs.* MWA 98.5%), DFS and major complication rates between these two groups. Another recent study involving treatment of 45 HCC with RFA and 66 with MWA (measuring up to 5 cm, mean 2.95 ± 1.03 in RFA, mean 2.90 ± 0.97cm in MWA) also demonstrated equal efficacy in tumor ablation and OS, with the microwave group showing a statistically lower rate of local recurrence ($p = 0.04$) [55].

MWA has been shown to compare well with RFA in regard to morbidity and mortality, with studies reporting mortality rates of less than 0.5% and morbidity rates around 3.0%. Among the reported, but infrequent, major complications were hemoperitoneum, portal vein thromboembolism, bile duct injury including bile leak and biloma, liver dysfunction, liver abscess, diaphragmatic injury and hemothorax [56].

IRE is a relatively new non-thermal ablative technique which employs multiple, rapid high-voltage pulses to disrupt the existing cell membrane potential, ultimately generating small defects in the lipid bilayer leading to loss of cell homeostasis and death. Because of its non-thermal nature, there is relative sparing of the surrounding parenchyma and structures including blood vessels and bile ducts, making IRE a practical alternative for tumors in close proximity to these structures. A meta-analysis of 16 studies performed by Scheffer et al. [57] found promising results for IRE treated hepatic tumors with complete response ranging between 67-100% at 3 months, and notably from 93–100% for tumors less than 3 cm. Additionally, stenosis or occlusion in the nearby vessels and bile ducts developed in only 8 of 129 treated liver lesions (6%).

Discussion

Currently, the best treatment option for cirrhotic HCC patients is OLT, however, success depends on tumor characteristics. In the United States, the one-year survival rate for non-HCC patients after OLT is 92% whereas patients transplanted outside the Milan Criteria have poor outcomes with a 5-year survival rate of 46%-60% [58]. In order to maximize the utility of liver allografts as a scarce resource, the United Network of Organ Sharing (UNOS) employs strict guidelines for the prioritization of patients with HCC as candidates for OLT. To be considered, patients must be within the Milan Criteria, and patients outside the criteria must be down staged via a treatment modality and maintained within the criteria until transplantation.

In 2002, Molmenti and Klintmalm described four risk factors on explant pathology which correspond to HCC recurrence and mortality after OLT: tumor size greater than 5 cm, vascular invasion, nodal metastasis, and poor histologic grade [9].

Liver targeted therapies in the form of TACE, percutaneous ablations (thermal and non-thermal) and TARE, have been used as bridging therapies in OLT candidates with HCC under the assumption that these modalities prevent progression of the disease and may maintain candidacy status during the waiting time for an organ offer [59]. However, there is no robust evidence that these liver targeted therapies are able to modify the four risk factors

mentioned above and benefit patient outcomes. Approximately 20% of HCC patients are removed from the waiting list before transplantation due to tumor progression [60]. There is some evidence that patients with complete tumor necrosis in response to a bridging therapy have a higher 5-year survival rate compared to patients with only partial response to therapy (86% *vs.* 66%), although this difference did not reach statistical significance [52].

Moreover, the financial burden of bridging LRT has not been addressed. HCC treatment is expected to be associated with high financial burden whether with transplant, resection or ablation.

Despite the lack of strong evidence to support the use of these therapies and the expected high financial burden, increasing use of these therapies for candidates waiting for an OLT with HCC has been reported by transplant programs. Approximately 255 (of 977) OLT candidates with HCC were reported to receive ablative therapy (AT) in 2003, and more than 50% reported having AT in 2006. Utilization of TACE has been gradually increasing, while there was a slight trend toward fewer cases of radiofrequency ablation (RFA) reported in 2006 [61].

Most importantly, there have been no large studies to truly compare patients with HCC who receive liver targeted therapy and patients who do not while waiting for OLT. Additionally, there are no data to support whether a single modality or combination of therapies is more beneficial to those patients awaiting liver transplantation.

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