Review Article

Bridging patients with hepatocellular cancer waiting for liver transplant: all the patients are the same?

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Abstract: Liver transplant (LT) is considered the best curative treatment for patients with cirrhosis and hepatocellular carcinoma (HCC) within Milan criteria. The possibility to perform LT in HCC patients is limited by the liver grafts supply; indeed, the shortage of donors often leads to a long time on waiting list and then to dropout because of tumor progression. Bridging therapies are neo-adjuvant treatments given to patients on LT waitlist, with the aim to prevent tumor progression and to reduce dropout rate. Many bridging modalities have been proposed. The choice of each treatment is based on the characteristics of the patient, liver function, comorbidities and on the number, dimensions and localization of HCC. This review article describes several types of bridging therapies, focusing on the indications for different kind of patients.

Keywords: Bridging therapy; hepatocellular carcinoma (HCC); liver transplant (LT); locoregional treatment (LRT)

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Hepatocellular carcinoma (HCC) is the fifth more frequent cancer worldwide and the most common primary liver tumor. Liver transplant (LT) is considered the best curative treatment for patients with cirrhosis and HCC within Milan criteria (1 tumor ≤5 cm and up to 3 tumors ≤3 cm). It removes all the liver affected by cancer and at the same time it treats the underlying liver disease, with a survival rate of 70% and a 5 years recurrence rate of less than 20%. Unfortunately, the applicability of LT for HCC patients is limited by the shortage of liver grafts, determining a longer time on waitlist and high dropout rate. Bridging treatments are neo-adjuvant antitumoral therapies given to patients on the waitlist for LT, affected by HCC within the criteria, with the aim to reduce the disease progression and therefore the dropout rate. Indeed, these treatments act as a "bridge" until a suitable donor organ becomes available. Most of bridging therapies are locoregional treatments (LRTs). Dropout rate for HCC progression increases in a time-dependent way (1) and evidences show higher dropout rates in patients with tumor >3 cm and an expected waiting time longer than 3–6 months (2). In different reports, if HCC is left untreated, the risk of drop out at 6 months and at 1 year has been estimated to be respectively 12% and 15–30% (3,4). Risk factors for dropout include: tumor diameter greater than 3 cm or multifocal disease, serum α-fetoprotein (AFP) level greater than 200 ng/mL, waiting time longer than 6 months and lack of response to bridging therapy (5). Although there are no randomized control trials (RCT) evaluating the efficacy of neo-adjuvant therapies in reducing dropout rate and improving survival after LT, LRT is accepted as the standard of care for patients expected to stay on the waitlist for more than 6 months. In patients with HCC within Milan criteria, bridging therapy is estimated to reduce dropout rate to 0–10%. A retrospective study

assessed the effectiveness of neo-adjuvant treatment in decreasing dropout rate and found that the 49% of patients with a complete response to LRT had a significant reduction in dropout at 3, 6, and 12 months (6). Other studies showed that bridge therapies are successful in keeping patients on the waitlist and they increase the likelihood of LT, specifically in longer waitlist time (7,8). The currently available evidence about survival benefit in HCC patients receiving pre-transplant LRT remains heterogeneous and contradictory. Even if some evidences indicate that bridging therapy can increase post-transplant survival rate (9), this statement is not confirmed by a recent large multicentric analysis. This retrospective study evaluated the impact of LRT on recurrence and survival after LT on 3,601 recipients with HCC within Milan criteria and did not demonstrate any advantage in terms of survival benefit and recurrence free survival (RFS) in patients treated with LRT, compared to patients not receiving LRT at all (10). The effectiveness of bridging LRT on improving post-transplant overall survival (OS) and RFS is limited to patients with a complete pathologic response of the tumor after LRT (10,11). To reduce dropout from the waitlist for tumor progression in HCC patients awaiting LT, a consensus statement recommends that bridging therapies should be considered for patients with 1 nodule of 2–5 cm or up to 3 nodules each ≤3 cm, expected to wait longer than 6 months to reduce dropout from the waiting list because of tumor progression. Different modalities have been proposed as bridging therapies, the most common is transarterial chemoembolization (TACE). Currently, any survival benefit has been demonstrated for any particular LRT modality, so no one form of treatment can be recommended over another (10,12).

Liver resection (LR)

LR is commonly used as primary curative treatment for HCC. OS after LR in cirrhotic patients is over 50% at 5 years and perioperative mortality is 2–3% (13,14). LR can be considered as a first line bridging treatment to LT. The theoretical advantage of surgery is a better control of tumor growth, as TACE and other LRT do not achieve complete tumor ablation as well as surgery. Moreover, the pathologic analysis of the resected specimen allows an evaluation of tumor biology and provides a selection of patients with risk factors of poor prognosis who are at major risk of early recurrence and should have a priority in LT waitlist (15). However, in most transplant Centers, for HCC patients waiting for LT, TACE and other LRT are preferred, mainly because LR, compared to non-surgical therapies, has higher costs and more complications and can only be performed in well-compensated liver disease.

TACE

TACE is the most widely used bridging treatment. A chemotherapeutic drug (commonly doxorubicin, cisplatin or mitomycin C), emulsified in lipiodol with embolizing material, is injected into the branch of the hepatic artery feeding the tumor, with the aim to induce hypoxemia and tumor necrosis. This technique has been enhanced by the introduction of drug-eluting beads (DEB-TACE), with higher dose and retention of chemotherapeutic drug into the tumor and reduction of systemic toxicity. In the histological examination, TACE achieves complete pathological response in less than 30% of cases. Many authors analysed the impact of TACE as bridging therapy to LT on dropout rates in waitlist, survival and recurrence after LT. The reported results of bridging therapy with TACE are controversial and no prospective RCTs have confirmed its efficacy in reducing dropout rates. Many authors demonstrated that a good response to TACE (necrosis >60%) is significantly related to an improved long-term survival after LT and a lower recurrence rate (16). Others did not find any significant advantage in overall and RFS after LT in HCC patients bridged with TACE (17,18). Despite various reports had suggested favorable long-term outcome in patients successfully bridged with TACE, the real benefit in terms of survival after LT remains questionable, nevertheless TACE remains a widely used technique in clinical practice.

Radiofrequency ablation (RFA)

RFA is an ablative technique that uses a radiofrequency electrode tip generating alternating current, that induces coagulative necrosis in the target tumor by thermal action, with temperatures of 60 to 100 ℃. It can be performed by intraoperative or percutaneous approach. RFA is known to be an effective curative treatment for patients with non-resectable HCC. When used as a bridging treatment, RFA reduces significantly the dropout rate (19). The success in achieving complete necrosis depends on the size of the target lesion: RFA for HCC with diameter of 2.5 cm or less lead to complete necrosis in up to 90% of cases. For lesions of 5 cm diameter or more, the remarkable necrotic effect is estimated less than 50% (19). Even if RFA is proven to be a

safe procedure, it has some limitations and complications. It should be avoided in subcapsular HCC and in nodules located near bowel loops or gallbladder and the tumor should be visualized by ultrasound. The 'heat-sink' effect may reduce RFA efficacy for tumors near the major vessels. Complications of RFA include thermal or mechanical damage, leading to rare but severe complications, such as acute liver failure, liver abscess, haemobilia. Tumor seeding is reported as a very rare complication (0.3–0.5%) (18).

Percutaneous ethanol injection (PEI)

PEI is the oldest technique for the percutaneous ablation of HCC, introduced in the 1980s to treat small HCC safely and effectively. At present, PEI is rarely used as bridging technique, while thermal ablation procedures [RFA or microwave ablation (MWA)] are currently preferred, because they need a small number of treatments and give better tumor control (20,21).

MWA

MWA is a percutaneous thermal ablation procedure that has been shown to be effective and promising as bridge therapy of HCC. As well as RFA, the lesion should be visualized by ultrasound for an exact localization. Compared to RFA, MWA leads to a larger volume of necrosis and it seems to be more effective in multifocal disease and for nodules located near large vessels, because of the lack of 'heat sink' effect. Many authors reported similar response rate with RFA (22,23) and a clear advantage of MWA versus RFA has not been demonstrated.

Irreversible electroporation (IRE)

IRE is a non-thermal ablative technique that uses high-voltage electricity to induce apoptosis of target cells by increasing irreversibly the membrane permeability. It also induces complete cell death even in lesions adjacent to large vessels, without the 'heat sink' effect seen in RFA. IRE should have a potential role in patients in waitlist, but currently there are few data about his use as bridging therapy. Cheng *et al.* report a high rate of complete necrosis for IRE used in the treatment of tumor <3 cm (24).

Transarterial radioembolization (TARE)

TARE is an intra-arterial therapy using microspheres coated with Yttrium-90 (Y90). This technique allows a high concentration of radioactive substance in the lesion, with minimum toxic damage to the surrounding liver parenchyma. It is also a safe procedure in case of portal vein thrombosis (25). Most of the current studies are focused on TARE used as downstaging therapy for patients with HCC out of the criteria, then there are not many studies about the role of TARE in bridging therapy. Compared with TACE, TARE seems to allow a good tumor response in shorter times and a longer time to progression, suggesting a potential advantage in bridging therapy. TARE is not indicated for all patients: before the procedure an assessment of the vascular anatomy is required and a mesenteric angiogram with 99Tc macroaggregated albumin should be performed.

High intensity focused ultrasound (HIFU)

HIFU is a totally extracorporeal ablative technique, that uses ultrasound beams to induce heat reaction, reaching 60 ℃ of temperature or more, leading coagulative necrosis in the HCC nodule. The heat damage to the tissues between the transducer and the target is reduced to minimum. Cheung *et al.* described the experience of HIFU used as a bridging therapy and observed an improvement of the rate of patients receiving bridging therapy in the waiting list and a reduction of drop-out rate (26,27). Further researches are needed to assess the real survival benefit after the LT in patients previously treated with HIFU. Before performing HIFU, it is necessary to assess the localization of the nodule by ultrasound. It is a safe procedure with minimal risk. Very rare but severe complications, such as bile duct injury, have been reported; minor complications such as skin and subcutaneous tissue injuries are described in many patients(28).

Stereotactic body radiotherapy (SBRT)

SBRT is an extracorporeal technique consisting in a high dose of radiations focused on the target lesion, needing few treatment sessions. It is an alternative bridging therapy for patients with decompensated liver function that would not be candidate to other bridging therapy (29). Data regarding the use of SBRT as a bridging treatment are scarce. Sapisochin *et al.* recently reported an intention to treat analysis about SBRT used as a bridging therapy in patient not eligible for other LRTs and observed similar drop-out rate with SBRT and RFA or TACE (30). It is proven to be a safe procedure for lesions <6 cm of diameter, even in those

Table 1 Main characteristics, indications and disadvantages of the different bridging techniques

Technique	Advantages	Limits
Resection	Potentially curative treatment; best results in left lobe and single subcapsular nodules	Unfeasible in patients with decompensated liver disease, severe portal hypertension or thrombocytopenia
TACE	More effective using the superselective technique, in well-vascularized nodules with large feeding arteries; possibility to treat multiple nodules	Unfeasible in patients with portal thrombosis (consider superselective approach), hepatic arteriovenous fistulas, renal failure or CTP C class
TARE	Possible better effectiveness than TACE in cases with multiple and large nodules; allowed in case of portal thrombosis	Less experience than TACE; high cost
RFA	More effective in nodules ≤3 cm	Risk of bleeding in patients with impaired clotting parameters or lesions located superficially; heat-sink effect: dangerous for nodules near the gallbladder, major vessels, bile ducts, or bowel loops
PEI	More effective in nodules ≤3 cm; more suitable in patients with impaired clotting parameters or lesions near the gallbladder or bowel	Less effective than RFA for nodules >2 cm
MWA	Possible better effectiveness than RFA in nodules ≥3 cm; safe procedure for nodules located near large vessels	Less experience with MWA than RFA; potentially dangerous in patients with impaired clotting parameters or with lesions located superficially or near the gallbladder, major bile ducts, or bowel loops
HIFU	Indication in case of portal thrombosis	Dangerous for lesions adjacent to the central biliary system
SBRT	Indication for nodules near the major bile ducts	Risk of bowel perforation

TACE, transarterial chemoembolization; TARE, transarterial radioembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; MWA, microwave ablation; HIFU, high intensity focused ultrasound; SBRT, stereotactic body radiotherapy.

localized near the central biliary system, where surgery or ablation cannot be performed (31,32).

Sorafenib

Sorafenib is an oral multi-kinase inhibitor, it delays the tumor progression by inhibiting angiogenesis. The significant efficacy of sorafenib in extending the time-to-progression in patients with advanced HCC is well demonstrated. Studies about Sorafenib used in bridging setting are limited. His effect as neo-adjuvant therapy has been often studied in association with TACE. TACE allows embolization of the tumor feeding artery and it leads to necrosis by local chemotherapeutic effect, in the same time sorafenib inhibit angiogenesis to delay the tumor progression and relapse. The use of sorafenib in combination with other bridging techniques have been described in clinical trials (33), even if the role of combination of bridging therapies is still to be determined.

Choosing the right treatment for each patient

Table 1 summarizes the main characteristics, indications and disadvantages of the different bridging techniques. Any treatment for HCC should be performed with the aim to reduce to minimum the risk of hepatic failure. Up to date, there are no RCT comparing their efficacy in the setting of LT and no guidelines are available to define which patients should receive bridging therapy. Currently, the choice is mainly based on Centre experience. Although the operator's practice has its importance, the method selected for bridging therapy has to be tailored on the conditions of the patient, considering also tumor features and stage. Basing on BCLC algorithm, different treatments are suggested.

Patients in very early stage (BCLC-0): good liver function (Child-Pugh A), single nodule less than 2 cm, without vascular invasion neither satellitosis (HCC T1 in TNM classification). These patients have an excellent outcome: 5-year survival after resection or transplantation is 80–90% and 70% after LRT. The risk of recurrence at 3 years is 3% (34). The choice of the bridging technique depends on portal hypertension and localization of the nodule. If MELD score is less than 10 and there is not portal hypertension, without thrombocytopenia, LR is the treatment of choice. In fact, LR can only be offered

to selected patients. Single subcapsular or exophytic HCC, or tumors in the left lobe are the best tumors to be treated with LR in bridging setting. There is no significant difference in post-operative complications and 3- and 5-year OS between cirrhotic HCC patients undergoing primary LT or secondary LT after LR (35). If performing LR is not possible, RFA, PEI or IRE can be considered, even if Clavien *et al.* assess the lack of evidence of usefulness of bridging treatments in patients with T1 HCC (12). Patients in early stage (BCLC-A): Child-Pugh class A or B, with single nodule or less than 3 nodules, each one with a diameter of 3 cm or less. In this category of patients bridging therapies mainly consist in LRT. RFA should be preferred in patients with single nodule less than 5 cm. The best effect of RFA as bridging therapy is shown in patients with small tumors (3 cm or smaller) with a waitlist time of less than 1 year (36). PEI seems to have lower efficacy than RFA and can be used in small HCC located in sites considered dangerous for RFA (for example near the bowel loops or the gallbladder). TACE is indicated in patients with one or more nodules and should be considered the treatment of choice for HCC between 3–5 cm, because nodules with 3 cm of diameter or more are better vascularized, with a large feeding artery, therefore the effectiveness of TACE appears to be better; whereas smaller HCC have not yet a completely developed arterial neoangiogenesis (14,37). In this class of patients, TARE should also be considered and some authors assess the potential advantage of this technique towards TACE, because it seems to need less treatments and the recurrence time is longer (38). Patients with ascites: even if BCLC algorithm does not indicate TACE for treatment of HCC, it has been considered anyway, in selected patients in waitlist, only if performed in superselective way. In case of portal thrombosis, TACE has always been considered not indicated, for the high risk of hepatic failure, but other studies have shown his feasibility as bridge therapy, only if superselective. In these patients TARE has been indicated as the better choice, it is described as a safer procedure, because it keeps minimum toxicity to the functional liver parenchyma. In patients in waitlist with HCC and Child-Pugh C cirrhosis, TACE is not indicated. Bridging therapy can be safely performed with TARE or HIFU, that had been shown to lead to good radiological responses, with minimum risk of worsening liver function (27). Every technique has his collateral effect towards liver parenchyma, biliary tree, venous structures of adjacent organs and this must be considered in the choice of the treatment. The presence of the "heath sink effect" in RFA can lead to incomplete ablation of nodules near the major vessels. RFA may be dangerous for lesions near the gallbladder or bowel, for the risk of biliary lesions, hemorrhage or gastrointestinal perforation. For lesions near the gallbladder or bowel, PEI seems to be safer than RFA. In the same way, SBRT is not indicated for lesions near the bowel, for his risk of bleeding and perforation (31). However, SBRT have the advantage to treat the lesions adjacent to the central biliary system, that are not suitable for LR or ablation. For lesions near major vessels, where RFA is contraindicated, MWA could be a safe treatment option (39).

Conclusions

Different techniques are currently in use as bridging therapies for LT, in order to decrease drop-out rate from waitlist. The selection of each therapy is based on liver function and tumor features, like localization, dimensions and number of nodules. Further studies have to be performed to assess the efficacy and feasibility of many of these neo-adjuvant therapies.

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Footnote

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