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Multimodal oncological approach in patients affected by recurrent hepatocellular carcinoma after liver transplantation

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Abstract. – OBJECTIVE: Hepatocellular Carcinoma (HCC) represents the fifth most common malignancy and the third cancer-related cause of death worldwide. Liver transplantation (LT) is an excellent treatment for patients with small HCC associated with cirrhosis. The purpose of this review is to investigate the possible strategies for the treatment of HCC recurrence after LT based on current clinical evidence.

MATERIALS AND METHODS: A systematic literature search was performed independently by two of the authors using PubMed, EMBASE, Scopus and the Cochrane Library Central. The search was limited to studies in humans and to those reported in the English language.

RESULTS: Thanks to the introduction of strict selection criteria, LT for HCC has achieved a survival rate of 85% at five years. However, the recurrence of HCC after transplantation remains a serious problem that affects about 20% of post-transplant cases. While most recurrences occur within the first 2 years, late recurrences have been described. The prognosis of recurrence is poor despite numerous proposals of the therapeutic option. Lower levels of immunosuppressive therapy and use of mammalian targets of rapamycin (mTORs) is a potential preventive strategy to reduce HCC recurrence post-Lt. Surgical resection and locoregional therapies (mainly TACE and RFA) play a very important role and are associated with improved survival. Conversely, multikinase inhibitors such as Sorafenib and their association with mTOR inhibitors play a role in cases of advanced HCC recurrence not suitable for the surgical or ablative approach.

CONCLUSIONS: Treating HCC recurrence is a multidisciplinary workup involving hepatologists, surgeons, oncologists and radiologists in order to offer a patient-tailored therapy.

Key Words:
HCC, Liver transplantation, Multimodal treatment, Recurrence, Chemotherapy, Immunosuppressive therapy, mTOR.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with an estimated incidence of one million cases per year[1,2]; being highly malignant, it is the third most common cause of cancer mortality, accounting for approximately 600,000 deaths annually worldwide, about 9.2% of cancer deaths[3,4].

The incidence of HCC seems to grow gradually because new cases are expected due to patients' long-term chronic viral hepatitis. Furthermore, it is estimated that the increase in patients with obesity and, consequently, nonalcoholic fatty liver disease (NAFLD) incidence, can be responsible of novel cases of HCC[5]. Moreover, a crucial role of the HIV TAT protein to drive hepatocarcinogenesis in patients with virus- or alcohol-mediated cirrhosis[6,7]. The etiological causes of this cancer are manifold, namely viral, inflammatory and genetic. It is well-known that hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse, and NAFLD are the major risk factors for hepatocarcinogenesis[8]. The surgical management proposed for the treatment of HCC in early stage varies from ablative therapies, liver resection, and liver transplantation. The choice of one of these therapies varies depending on both liver function and the number of neoplastic nodules.

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Surgical resection is the treatment of choice for patients with compensated liver function without evidence of cirrhosis[9]. However, hepatic resection is only suitable in a small number of patients with HCC because of impaired hepatic reserve and, frequently, a condition of multifocal disease at the time of diagnosis[10]. In the case of cirrhosis (Child-Pugh class B and C) and multiple nodules, liver transplantation is the only option available[11,12]. Liver transplantation (LT) is a treatment that works at two levels: oncological and pathophysiological. Total hepatectomy during transplantation is certainly the most radical cancer treatment since it removes all the tumor foci, along with any satellite nodules and dysplastic foci, with the widest margin possible. From a pathophysiological point of view, LT restores the normal portal flow overcoming all the negative consequences of portal hypertension. However, the application of this ideal technique is severely limited by the lack of organs and by the disease progression in the waiting-list. In fact, the international guidelines have limited the application of liver transplantation in patients with HCC with an expected 5-year survival greater than 50% or with an expected survival at five years equal to that of transplants performed for benign disease.

The initial experiences of liver transplantation for HCC were disappointing; these poor results were related to an inadequate selection of patients for transplantation. In 1996, Mazzaferro et al[13] published a study of great scientific importance: in a selected cohort of 48 patients they demonstrated a 4-year survival of 85% and a post-transplant recurrence of 8% through the use of restrictive selection criteria, subsequently called Milan criteria (a solitary lesion < 5 cm or multiple lesions no more than three in number, none of which are larger than 3 cm in the absence of macrovascular invasion and metastasis).

Other researches have confirmed these promising results, and the criteria have therefore been adopted by most centers and used by United Network for Organ Sharing (UNOS) as the principles of selection of patients on the waiting list for transplantation for HCC. In UNOS the staging classification of HCC is further divided into stage T1 and T2 where T1 identifies a single tumor < 2 cm and T2 a single tumor measuring 2 to 5 cm or 2/3 nodules each equal to or less than 3 cm in size.

Recent studies suggest that these criteria could be expanded without significantly impacting long-term served. In 2000, Yao et al[14,15] proposed a modest expansion of the criteria. The transplantation team in San Francisco reported 88% 5-year recurrence-free survival in a cohort of patients whose liver explant presented one tumor measuring ≤6.5 cm or two to three nodules with the largest lesion measuring ≤4.5 cm, and a total tumor diameter of ≤8 cm, defining them as the San Francisco (UCSF) criteria. A multicenter analysis of 1556 patients with HCC[16], of whom 1112 exceeded Milan Criteria, has led to the definition of the "up to seven" criteria (with seven as the sum of the size of the largest tumor [in cm] and the number of the tumors); within this extended criteria, patients can achieve a 5-year survival of 70% (Table I).

All the aforementioned criteria described in the literature are based on morphological criteria (size and number) of tumor nodules at imaging, not always corresponding to the actual pathological results[17,18]. Furthermore, many authors consider these criteria as inaccurate surrogates of the biological behavior of the tumor. Currently, the microvascular invasion is considered the most accurate predictor of post-LT tumor recurrence[19]. Unfortunately, this parameter has no practical use since it can only be known on histological analysis of the explanted liver. On the other hand, the tumor size and the number of nodules positively correlate with microvascular invasion[20].

The allocation of organs based on the MELD model (model for end stage liver disease) that assesses the likelihood of risk of death on the waiting list was adopted in the United States by United Network for Organ Sharing (UNOS) in 2002[21-23]. This model was applied to patients on

Table I. Selection criteria for liver transplantation in patients with HCC.

Selection criteria of liver transplantation for HCC	
Milan Criteria	1 tumor ≤ 5 cm or a maximum of 3 tumors each ≤ 3 cm
UCSF criteria	1 tumor ≤ 6.5 cm or max. 3 tumor nodules each ≤ 4.5 cm and sum of tumor diameters ≤ 8 cm
Up-to-seven criteria	Sum of maximal tumor diameter and number of tumor nodules ≤ 7

HCC, hepatocellular carcinoma; UCSF, University of California at San Francisco.

the waiting list and with HCC, although many authors consider it inadequate because the risk of tumor progression over the criteria of transplantability is greater than the risk of death during the time on the waiting list. Therefore, in the US patients with HCC are prioritized by assigning an additional score to compete with others suffering from non-neoplastic diseases. However, it has been estimated that the proportion of patients transplanted for HCC has increased by about six times[24]. In 2005, due to the increase in the number of patients transplanted for HCC, and given that the risk of neoplastic progression while on the waiting list appeared lower than previously calculated UNOS determined that patients with T1 HCC no longer receive extra MELD points, while T2 HCC patients receive 22 extra Meld points[25].

HCC recurrence after liver transplant is estimated to show up in 5% to 30% of cases and occurs more frequently in the two years following transplantation[26,27]. The management of this disease contemplates various treatment modalities: surgical liver resection, ablative therapies, immunosuppression and target tyrosine kinase inhibitor. Few studies on the management of post-transplant recurrence of HCC have been performed. The purpose of this review is to summarize the strongest clinical evidence in the treatment of HCC recurrence in LT patients.

Materials and Methods

Literature Search

A systematic literature search was performed independently by two of the manuscript's authors using PubMed, EMBASE, Scopus and the Cochrane Library Central. The search was limited to studies in humans and to those reported in the English language. No restrictions were set for the type of publication. Participants of any age and sex who underwent treatments for hepatocellular carcinoma recurrence after liver transplantation were included in this study.

The following MESH search headings were used: "hepatocellular carcinoma" OR "hcc" OR "hepatoma" AND "recurrence" AND "TACE" OR "radiofrequency ablation" OR "pei" OR "microwave" OR "radioembolization" OR "local treatment" OR "surgery" OR "resection" OR "hepatectomy" OR "Sorafenib". An extensive crosschecking of the reference lists of all retrieved articles that fulfilled the inclusion criteria was performed to enrich the search. For all of the databases, the last search was run on June 1st, 2016.

Study Selection

The same two authors screened the titles and abstracts of the primary studies that were identified in the electronic search. The following criteria were adopted for inclusion in this review: (1) Studies on treatment of HCC recurrence after liver transplantation, (2) Studies comparing the outcomes of different treatments; (3) Studies reporting at least one perioperative outcome; and (4) If more than one study was reported by the same institute, only the most recent or the highest quality study was included.

The following exclusion criteria were set: (1) Studies focusing on HCC recurrence without liver transplantation; (2) Studies in which it was impossible to retrieve or calculate data of interest.

The main data were extracted as follows: (1) First author, year of publication and study type; (2) Number and characteristics of patients and (3) Treatment outcomes including hospital stay, mortality rate, recurrence rate, 5-year overall survival and 5-year disease free survival. All relevant texts, tables, and figures were reviewed for data extraction and, whenever further information was required, the corresponding authors of the papers were contacted by e-mail.

Discrepancies between the two reviewers were resolved by consensus discussion or with the opinion of the Senior Author (FDB).

Results

Strategies to Prevent HCC Recurrence

Characteristic Features of Recurrence

Tumor recurrence is the most important cause of death in patients with HCC undergoing transplantation, occurring in 5 to 30% of cases. The recurrence of HCC after liver transplantation remains an open issue because, despite the strict criteria of selection, it has a considerable effect on survival[28,29].

Post-LT recurrence typically occurs in 80% of cases within two years, although very late recurrences have been described at 5 years. A recent systematic review that included 61 studies showed that the average rate of recurrence post-LT was 16%. The median time to recurrence after transplantation was 13 months (range 2-138). 51%

of LTs were classified as outside of Milan Criteria at pathological staging. The overall median survival after HCC recurrence was 12.97 months (range 0.1-112.5)[30].

HCC metastasis typically involves the liver graft, lung, bone, abdominal lymph nodes, adrenal glands and also the peritoneum in order of decreasing frequency. Multiorgan and extrahepatic metastases are common (up to 50-70%), while intrahepatic metastases account for less than 30%. The latter also have a better prognosis because they can be treated with ablative therapies or surgery with radical intent[31].

Recurrence of HCC after liver resection generally involves different mechanisms: inadequate resection margins (positive margin R1), intrahepatic hematogenous tumor cell spread, de novo HCC (multifocal HCC or dysplastic nodules) in the background of cirrhosis. However, the situation appears different in the transplant setting. Molecular biology researches demonstrated that perioperative or intraoperative hematogenous spread is the most important pathway. Although lymphatic metastases and peritoneal spread have been described, it has been suggested that circulating tumor cells reach the graft through the hematogenous route, which represents a positive environment for cell growth, through specific adhesion molecules (homing pattern)[32,33].

Prognostic factors of recurrence after transplantation have been extensively studied and have been used over time to select patients for liver transplantation. In addition to the known characteristics of tumor volume (size and number of neoplastic nodules), tumor differentiation, vascular invasion and biochemical markers such as α-fetoprotein (AFP) and Des-γ-carboxyprothrombin (DEC) are important prognostic factors[34]. Integrated prognostic models have been proposed in order to predict the behavior of HCC after transplantation, but none of them is truly able to identify the risk accurately[35,36].

Currently, the microvascular invasion is considered the most accurate predictor of post-LT tumor recurrence. Unfortunately, this parameter has no practical use since it can only be known on histological analysis of the explanted liver. On the other hand, tumor size and number of nodules positively correlated with microvascular invasion. Several reports have shown that the size and the number of tumor nodules have a negative prognostic effect on survival post-LT[37]. In the Metroticket study[16], the risk of tumor recurrence increased proportionally and linearly with the increasing tumor diameter, while the risk of tumor recurrence increased with the increasing number of nodules, until it reaches a plateau (non-linear behavior). Toso et al[38] suggested that patients with a total tumor volume of fewer than 115 cm^3 and AFP levels lower than 400 ng/mL had satisfactory post-transplant survivals.

It was observed that tumor differentiation is an independent predictor of tumor recurrence, which is also inversely correlated with vascular invasion[39]. The tumor grading represents a direct indicator of biological aggressiveness of the disease and is probably one of the most accurate prognostic indicators of recurrence. For this reason, many authors have suggested performing a biopsy pre-LT in order to assess the histological grade[40]. This approach is controversial: some studies indicate a low level of accuracy in the evaluation of the grading through the biopsy, although some of these have often been conducted in patients with large tumors, where the great histological heterogeneity of these lesions is known. The application of the tumor biopsy pre-LT for tumor differentiation grade has been limited up to now by a number of factors, including the risk of needle track seeding and its inaccuracy when performed prior to transplantation[41]. Saborido et al[42] reported that a significantly higher chance of HCC recurrence came from fine needle aspiration biopsy before LT (31% *vs.* 5.9%, $p = 0.003$). In addition, this risk appears quite limited when one considers the potential benefit of knowing this information prior to transplantation. Moreover, in a recent French study it was shown that preoperative tumor biopsy does not affect the oncologic outcomes of patients with transplantable HCC; therefore, there is currently no indication to restrict liver biopsy in doubtful situations[43]. According to the diagnostic algorithm of the American Association for the Study of Liver Diseases (AASLD), the diagnosis of HCC is considered reliable when the tumor characteristics were concordant with the two imaging techniques, while the tumor biopsy was confined to doubtful cases, i.e. nodules without arterial enhancement (hypervascularity) or no wash-out in tardive phase.

In a meta-analysis of 9 studies for a total of 1198 patients, a significant correlation between vascular invasion, not well-differentiated HCC, tumor size > 5 cm, HCC exceeding the Milan criteria, and HCC recurrence post-transplant was shown[44].

However, understanding the interaction and interdependence between the tumor size, degree

of differentiation, and microvascular invasion is complex. Since not all cases of recurrence are always related to size or to differentiation, new gene markers that accurately predict tumor biology are needed in order to select patients in a more accurate fashion[45,46].

The molecular profile of HCC is a promising but still very expensive approach, and it remains a field of experimental research in predicting HCC recurrence. In a cohort of HCC patients treated with hepatic resection or liver transplant, three clusters of micro RNAs were identified[47,48]. microRNAs (miRNAs) have been proposed as a prognostic predictor in HCC as well. miRNAs play vital roles in mediating the expression of proteins by regulating the transcription or degradation of target mRNAs. In HCC, a number of miRNAs have been associated with survival or response to chemotherapy such as Sorafenib or doxorubicin[46]. However, tumor recurrence-related microRNAs (miRNAs) in hepatocellular carcinoma (HCC) following LT are not clear yet. A recent study[49] suggesting a different miRNA expression pattern between HCC samples of patients with recurrence and those without recurrence proposed that this six-miRNA signature may serve as a biomarker for prognosis of HCC patients following LT.

Chen et al[50] identified miR-203 as a novel prognostic marker in HCC patients who have undergone LT (n = 66). Indeed, in their study, it was found that miR-203 expression was low in tumor tissues of patients (n = 16) with post-LT HCC ecurrence in comparison with those in patients without recurrence (n = 50; $p = 0.003$).

Management of HCC on the Liver Transplant Waiting List

HCC patients awaiting transplant are referred to loco-regional treatments (mainly trans-arterial chemoembolization or radiofrequency ablation) in order to prevent the risk of tumor progression. As a matter of fact, drop-out for neoplastic progression is the most common cause of de-listing in patients with HCC. While the purpose of "bridging" therapy is to prevent the progression of the tumor, downstaging protocols aim to reduce the tumor mass within the transplant criteria[51-53].

The loco-regional treatments used with increasing frequency prior to transplantation include percutaneous injection of ethanol (PEI) or acetic acid (PAI), radiofrequency ablation (RFA), trans-arterial embolization (TAE) or trans-arterial chemoembolization (TACE), and radiation radioactive microspheres[54,55].

The function of these techniques is to induce necrosis of the tumor while preserving the surrounding healthy liver parenchyma. RFA under ultrasound was applied in the treatment of HCC, not amenable of liver resection or transplantation.

RFA causes tumor necrosis, and it can be performed percutaneously, or via laparotomy or laparoscopy. Its effectiveness is greater in treating nodules under 3 cm of diameter away from the portal vessels, whereas larger tumors require multiple applications. The main limitation is the partial effectiveness of this technique when the tumor is nearby large vessels, in the case of subcapsular nodules or in the vicinity of intestinal loops. However, PEI, microwave ablation (MWA) and RFA represent the three most widely used ablative techniques for the treatment of HCC less than 5 cm in diameter and/or with less than 3 tumoral lesions[56-58].

TACE is the standard of care for patients with preserved liver function and asymptomatic, non-invasive multinodular hepatocellular carcinoma (HCC) confined to the liver[59].

It has a dual mechanism: (1) occluding the vascular branches that feed the tumor and (2) conveying cytotoxic agent inside the tumor. The principle is based on the fact that HCC needs a vascular blood circulation for its growth.

Several studies have shown the efficacy of TACE in preventing tumor progression and drop-out in HCC patients on the waiting list. Other groups[60-64] argued that the response to TACE will need to better select candidates for LT.

In a study by Kim et al[65], one hundred seventy-three patients underwent TACE and imaging to assess response prior to LT. Five-year HCC recurrence rate was 5.3% in patients responding to TACE, *vs.* 17.6% among patients who did not respond (p=0.014). In a multivariate analysis, independent predictors of recurrence pre-LT were the response to TACE and the largest radiologic size of the tumor (> 3 cm *vs.* ≤ 3 cm).

Selected patients with HCC (stage III and IV) who are not candidates for transplantation can be "downstaged" through the use of neoadjuvant loco-regional therapy within Milan criteria in order to be transplanted. However, transplant benefits in patients undergoing downstaging must be balanced with the risk of removing organs to patients on the waiting list[59,66,67].

In a retrospective analysis from San Francisco University of 168 patients, a survival benefit was observed in patients with T2 or T3 HCC who received preoperative loco-regional therapy. The 5-year recurrence free survival was 94% in 85 patients, whereas patients who did not receive pre-LT ablation had a 5-year recurrence free survival rate of 81% ($p = 0.049$). The treatment benefit, according to 5-year recurrence-free survival, appeared greater for pathologic T3 (85.9% *vs.* 51.4%; $p = 0.05$) than T2 HCC (96.4% *vs.* 87.1%; $p = 0.12$)[68].

As recently highlighted by our group, the complete absence of HCC at explanted liver after loco-regional therapies is associated with a good post-transplant survival and a reduction in the rate of HCC recurrence. In our study, fifty-three (25.2%) patients did not show any evidence of active residual HCC in the native liver (Group NVH), whereas 157 (74.8%) patients showed viable HCC (Group VH) after loco-regional therapy. HCC recurrence occurred in none of the patients in the Group NVH (0%) and the 25 (15.9%) patients in Group VH ($p = 0.003$). The results of multivariate analysis showed that existence of HCC pathologic findings outside the University of California-San Francisco criteria ($p = 0.001$) and the presence of viable HCC ($p = 0.003$) were independently associated with HCC recurrence[69].

Treatment for HCC Recurrence After LT

Surgery and Ablative Therapy

While treating HCC is now well coded in the pre-transplant setting with therapeutic diagnostic algorithms, in which the extent of the tumor and the conditions in the underlying hepatic function guide therapeutic choices, the literature contains few reports regarding the treatment of post-transplant recurrence[70-72].

The multifactorial nature of tumor recurrence is the main limiting factor in surgical therapy[73]. A radical oncological resection is only possible in well-selected cases, as the majority of recurrences are metastatic and extrahepatic[74]. Theoretically, all therapeutic modalities used in the treatment of HCC can be applied in the treatment of HCC recurrence after transplantation. Although HCC recurrence is considered a systemic disease, aggressive treatment is generally reserved for patients with limited recurrence and with good liver function[75]. However, transplant patients are considered complex because they are immunocompromised by immunosuppressive therapy to treat rejection, at risk of developing infections and de novo neoplasms. Interventional radiological procedures such as TACE may be more difficult due to the presence of different vascular patterns after LT. The patient may also have dense adhesions to the hepatic hilum that make both dissection and liver resection extremely complex[76].

While patients with the disseminated disease are not candidates for loco-regional treatments, surgical approaches have been reported for the treatment of intrahepatic metastasis or extrahepatic metastases confined to a single organ[77]. Hepatic resection of metastatic HCC can be successfully applied in selected patients[78]. Liver resection for late recurrence (> 24 months) is associated with long-term survival. In contrast, early relapses are associated with poor prognosis. In the study by Valdivieso et al[79], surgical resection could be performed in 11 of 23 (42%) patients with HCC recurrence with a survival of 32.2 months *vs.* 11.2 months in patients with or without surgical resection ($p < 0.001$). The median time to recurrence was 23.4 months in patients undergoing LT and fulfilling Milan Criteria (n = 182). However, surgery in these patients is associated with a high rate of mobility since it can be technically more complex than routine procedures. Nevertheless, when applicable, liver resection can have good results in selected cases. As a matter of fact, the study by Royaie et al[80] identified solitary tumors less than 5 cm, good tumor differentiation and absence of bone metastases as prognostic factors of good outcomes. Five patients in this work were treated with liver resection, while 3 patients received RFA, all for intrahepatic recurrence. Other patients who had relapsed underwent extrahepatic lung resection (7 pts), adrenalectomy (3 pts), and resection of the chest wall (1 pt). Although 15/19 patients had a re-recurrence, the 5-year post-transplant survival was 47%.

Resection of HCC metastasis has been variously applied in cases of lung recurrence achieving complete resections (R0). Surgery has been accepted as the first treatment for pulmonary metastases after LT for HCC for some time. Studies have confirmed that surgery is effective, and survival is reported to be between 24% and 78% at 3 years, with median survival ranging from 21 months to 29 months. However, surgical resection of isolated metastasis following LT for HCC is limited to a few studies or case reports worldwide[81,82].

The literature contains a few anecdotal cases of transplantation for HCC recurrence for which each type of conclusion seems impossible[26].

Radiofrequency ablation (RFA) is a well-established treatment option applicable to cases of resectable or unresectable HCC; it has been shown that in cases of early HCC the results of RFA are similar to those of liver resection[83].

Koh et al[84] reported a recurrence rate of HCC after LT of 16% (78 out of 486 patients): 15 patients underwent surgical resection and 11 patients were treated with RFA. The remaining 52 patients received conservative therapy. The 1-, 3-, and 5-y overall survival rates were 92%, 51%, and 35% for the patients treated with surgery and 87%, 51%, and 28% for the patients who received RFA. Corresponding 1-, 3-, and 5-y recurrence-free survival rates were 83%, 16%, and 16% for the patients treated with surgery and 76%, 22%, and 0% for the patients who received RFA, respectively. There was no significant difference in overall survival or recurrence-free survival between the surgical resection group and the RFA group ($p = 0.879$, $p = 0.745$)[84].

MWA is a relatively new method of thermal ablative technique and is an effective treatment option for both primary and secondary liver malignancies, with survivals comparable with those of liver resections. MWA is also gaining popularity worldwide and is currently the most widely used treatment for unresectable hepatic malignancies[85]. With a cooled-tip electrode, MWA produces necrotic effects comparable to RFA without damaging soft tissues along the electrode track. In a recent study[86], 11 patients underwent MWA for intrahepatic HCC recurrence after LT. The MWA technique efficacy rate was 100% after the second cycle. Local tumor progression was identified in three cases (15.8%) at 1, 3 and 7 months after MWA. The 12 and 24 months accumulative survival rates were 30.7% and 15.3%, respectively; the average survival time was 17.3 months (3.5-33 months).

High-intensity focused ultrasound (HIFU) ablation is a relatively new and totally extracorporeal treatment for unresectable HCCs. Cheung et al[87] reported the outcomes of HIFU for the treatment of HCC before liver transplantation in 10 patients as compared to 29 patients who received trans-arterial chemoembolization, and found that HIFU was effective (90% had a complete response, 10% a partial response), with none of the patients on the liver transplant list (n = 5) dropping out.

In conclusion, isolated liver metastases account for 15%-20% of patients in most series, and represent the pattern of recurrence in which loco-regional therapies are applicable with success.

Trans-Arterial Chemoembolization (TACE) – Radio-Embolization

Another potential treatment for intrahepatic HCC recurrence is intra-arterial therapy with trans-catheter arterial chemoembolization (TACE)[62,88]. TACE is often used as a bridge treatment in patients awaiting liver transplantation, with good results. However, repeated cycles of TACE before transplantation can cause vascular changes in these patients, and specific complications of LT such as anastomotic stenosis could preclude the use of this technique[89]. Despite these potential limitations, TACE is one of the most commonly used techniques in the treatment of HCC recurrence post-transplant[90,91]. It has been shown that TACE is as effective as liver resection in the treatment of recurrent HCC after hepatectomy[59]. Lo et al[92] demonstrated good tumor response in patients treated with TACE; in fact, the overall survival at 1-3 years was 57% -26% *vs.* 32% and 3% respectively in the TACE group vs. the control group ($p = 0.002$). In the study by Ko et al[93] 28 patients with HCC recurrence after living donor LT and treated with TACE (2.5 cycles) were evaluated for the degree of tumor response: 68% achieved a 25% reduction of tumor volume. However, intrahepatic or extrahepatic metastases occurred in 21 out of 28 treated patients at the three-month follow-up, with a median survival of nine months. In this study, 28 patients had 1-, 3-, and 5-year survival rates of 47.9% 6% and 0% respectively, showing that the recurrence of HCC is a disseminate disease that would be best treated with a systemic therapy rather than loco-regional treatment. Although this procedure by Ko et al[94] was not burdened by any morbidity, other authors demonstrated a high risk of ischemia and necrosis of the liver after TACE.

Radiation therapy is another treatment used for recurrence of unresectable HCC and extrahepatic metastases, since the tumor is sensitive to radiation. The improvements in radiation techniques have allowed the application of stereotactic approach in the treatment of unresectable HCC not amenable to locoregional treatment. Several trials have shown good control in the rate of tumor growth and palliation of distant metastases. Yashimita et al[95] explored the usefulness

of radiotherapy in 28 patients with abdominal lymph node metastasis. These patients received a dose daily fractionated 2.0 of 60 Gy; a total of 18 (64%) and 5 patients (18%) achieved partial and total responses, respectively.

Internal radiotherapy means the delivery of Radioisotopes either percutaneously or through trans-arterial approach. Yttrium-90 (Y90) is applied to unresectable HCC by intra-tumoral injection of glass microspheres by the percutaneous route to assess the hepatic artery. This latter technique has in recent years gained popularity, especially in cases of large HCC or those with portal vein thrombosis[96,97]. This approach, called radio-embolization, is based on the different arteriolar density between the hypervascular HCC and the normal liver parenchyma. Arterially administrated Y90 microspheres depose selectively in tumor nodules, limiting the dose taken up by surrounding normal liver. This technique was proven useful for the majority of patients with HCC as most of them present in advanced stages, beyond potentially curative options (resection/liver transplantation). Y-90 microspheres can be used in large tumors with downstaging intent, in patients with portal venous thrombosis due to tumor invasion and as palliative therapy[97-99].

Immunosuppressive Therapy – mTOR

Proliferation signal inhibitors constitute a new class of immunosuppressive drugs that belong to the family of mTOR inhibitors (mammalian Target of Rapamycin). Two drugs in this family – Sirolimus and Everolimus – are used for the prevention of rejection in recipients of solid organs[100,101]. mTOR have an antineoplastic effect, mainly anti-proliferative and antiangiogenic through the inhibition of tumor growth and cell survival[102,103]. A number of studies have shown that the mTOR inhibitors Everolimus and Sirolimus suppress cell proliferation and tumor growth in animal models of HCC. It was also demonstrated that their use is associated with a significant reduction of the risk of cancer de novo incidence after kidney transplantation. mTOR inhibits the PI3K/AKT/mTOR pathway which is altered in the process of hepatocarcinogenesis[104]. According to studies in experimental models, the mTOR pathway appears altered in half the cases of HCC[105].

In terms of a preventive effect after liver transplantation for HCC, data from retrospective studies and non-randomized prospective analyses, in which patients received an mTOR inhibitor with concomitant calcineurin inhibitor therapy, have shown that HCC recurrence rates and overall survival may be improved compared to a standard calcineurin inhibitor regimen[106-108].

Two recent meta-analysis[109,110] have shown that Sirolimus is associated with significantly lower HCC recurrence rates, compared with calcineurin inhibitor-sparing regimens (CNIS). In the first meta-analysis including three studies with 103 patients and 129 patients on Sirolimus or CNIS-based immunosuppression, Sirolimus was associated with a significantly lower risk of HCC recurrence (OR: 0.42 95% CI: 0.21-0.83, $p = 0.01$). These results were confirmed in the recent meta-analysis by Cholongitas et al[111], in which 3666 HCC liver transplant recipients from 42 studies met the inclusion criteria. Patients under CNIS developed HCC recurrence significantly more frequently, compared with patients under mTOR inhibitors (448/3227 or 13.8% *vs.* 35/439 or 8%, $p < 0.001$). Patients on Everolimus had significantly lower recurrence rates of HCC, compared to those on Sirolimus or CNIS (4.1% *vs.* 10.5% *vs.* 13.8%, respectively, $p < 0.05$), but Everolimus-treated recipients had a shorter follow-up period (13 *vs.* 30 *vs.* 43.2 months, respectively) and had more frequently been transplanted for HCC within Milan criteria (84% *vs.* 60.5% *vs.* 74%, respectively, $p < 0.05$).

Data from *in vitro* studies and animal models clearly demonstrate that immunosuppressive therapy with CNI increases tumor growth through various mechanisms: decrease in the recognition of malignant cells to the immunosuppressive effect, increased invasiveness of cancer cells through reduced transforming growth factor B, increased angiogenesis by stimulation of vascular endothelial growth factor[112,113]. Other immunosuppressive agents such as anti-metabolites show little effect on the growth and cell proliferation. Indeed, in the studies by Rodríguez-Perálvarez et al[114], higher exposure to calcineurin inhibitors within the first month after LT (mean tacrolimus trough concentrations > 10 ng/ml or cyclosporine trough concentrations > 300 ng/ml) was associated with increased a risk of HCC recurrence (27.7% *vs.* 14.7% at 5 years; $p = 0.007$). High exposure to calcineurin inhibitors was an independent predictor of HCC recurrence by multivariate analysis, whereas HCC recurrence was not influenced by the use/non-use of steroids and antimetabolites ($p = 0.69$ and $p = 0.70$ respectively), and was similar with tacrolimus or cyclosporine ($p = 0.25$).

In the Silver Study[115], a prospective randomized international trial, 525 LTx recipients with HCC were randomized 4 to 6 weeks after transplantation to a group on mTOR-inhibitor-free immunosuppression (group A: 264 patients) or to a Sirolimus-containing immunosuppression group (group B: 261). Recurrence-free survival (RFS) was 64.5% in the group A and 70.2% in the group B, with no significant difference at study end (p = 12:28). However, group B showed better RFS 3 years after transplantation (HR, 0.7; 95% CI, 0:48 to 1:00). Interestingly, subgroup (Milan Criteria IN) analyses revealed that low-risk patients, rather than high-risk patients, benefit more from Sirolimus. Serious adverse event numbers were similar in groups A (860) and B (874). Sirolimus in LTx recipients with HCC improves RFS and OS in the first 3 to 5 years, especially in low-risk patients, but does not improve long- RFS term beyond 5 years.

Moreover, co-administration of an mTOR inhibitor could permit lower dosing of chemotherapeutic agents in HCC management, and trials in the non-HCC transplant population are exploring combined use with various agents including Sorafenib, the vascular endothelial growth factor inhibitor bevacizumab and conventional agents[116].

Chemotherapy-Sorafenib

Sorafenib is an oral multi-tyrosine kinase inhibitor exhibiting antitumor and antiangiogenic activity (including VEGFR1, VEGFR2, VEGFR3 and PDGFR-α, PDGFR-β, c-KIT, Raf-1, and BRAF); it was approved as a first-line treatment for advanced HCC. The activation of the RAS/mitogen-activated protein kinase pathway is commonly impaired pathway in the carcinogenesis of HCC tumors and appears crucial in promoting cell proliferation and survival of cancer cells[117,118].

The SHARP trial[119], a randomized phase III trial *vs.* placebo conducted in patients with metastatic or locally advanced HCC on cirrhosis (Child-Pugh A), demonstrated a benefit in terms of overall survival (10 *vs.* 7.9 months for Sorafenib *vs.* placebo) and progression-free survival (5.5 months *vs.* 2.8 months). A similar overall survival benefit from Sorafenib was noted in a second phase 3 trial, carried out in the Asia-Pacific region, with similar entry criteria and treatment plan. In this study, which enrolled 226 patients, those in the Sorafenib arm had a median survival of 6.5 months compared with 4.2 months for those on placebo (p = 0.014), respectively[120].

To explore more targeted agents for advanced HCC, Sunitinib and Brivanib have been investigated and compared with Sorafenib as first-line therapy in phase III trials. Results showed that Sunitinib and Brivanib were not superior regarding OS. Thus, the latest National Comprehensive Cancer Network (NCCN) guidelines recommended Sorafenib as the standard first-line therapy for advanced HCC with Child-Pugh A liver function.

Since the introduction of Sorafenib in 2008, there has been an explosion of interest in assessing its effectiveness in patients with recurrent hepatocellular carcinoma after hepatectomy or LT. Some groups have reported their experience with Sorafenib in combination with m-TOR immunosuppression in the treatment of HCC after transplantation[121,122]. A cohort study[123] of 31 patients who suffered from HCC recurrence after liver transplantation was designed to evaluate the safety and preliminary efficacy of the combined use of a mammalian target of rapamycin (mTOR) inhibitor and Sorafenib. In this setting, the immunosuppressive therapy was changed to mTOR inhibitors, and systemic treatment with Sorafenib was initiated. The overall response rate according to the Response Evaluation Criteria in Solid Tumors was 3.8% (1/26), and there was sustained stabilization of the disease in 13 additional cases (50.0%). The median overall survival was 19.3 months and the median time to progression was 6.77 months (95% CI = 2.3-11.1 months). In a recent study from Italy, the outcomes of Sorafenib treatment for post-LT HCC recurrence were significantly better than those of best medical care, with median patient survival from recurrence: 21.3 months *vs.* 11.8 months, p = 0.0009; median patient survival from untreatable presentation or progression: 10.6 months *vs.* 2.2 months, $p < 0.001$.

The most frequent symptoms reported are gastrointestinal (diarrhea), hand-foot skin reaction, fatigue, and hypertension. Hand-foot skin reaction, however, seems more pronounced in transplant patients[124-125]; four cases of death related to the association of Sorafenib and mTOR agent are reported in the literature. It is highly desirable during treatment with Sorafenib and mTOR immunosuppression therapy to closely monitor liver function, kidney and bone marrow, as well as the level of immunosuppressive drugs to prevent potential toxic interactions. Traditional chemotherapy has a very limited scope in HCC as cytotoxic agents traditionally have a marginal effect on this tumor[126].

Conclusions

Despite careful selection of patients undergoing transplantation, HCC recurrence remains a devastating problem that affects about 20% of patients[127]. The prognosis is poor in most patients since relapse generally involves multiple organs. Recurrence represents a systemic cancer spread. Therefore, the association of systemic therapy (Sorafenib) with the use of mTOR inhibitors and surgical or ablative approaches should be considered. Better survival rates are observed in patients amenable of surgical or ablative therapy with radical intent for their recurrence.

At the current state of the literature, the lack of guidelines or strong evidence suggests that the most effective treatment for the individual patient should be built within a multidisciplinary team.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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