Posttransplant Management of Recipients Undergoing Liver Transplantation for Hepatocellular Carcinoma. Working Group Report From the ILTS Transplant Oncology Consensus Conference

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Abstract. Although liver transplantation (LT) is the best treatment for patients with localized hepatocellular carcinoma (HCC), recurrence occurs in 6%–18% of patients. Several factors, particularly morphological criteria combined with dynamic parameters, known before LT modify this risk and combined in prediction models may be used to stratify patients at need of variable surveillance strategies. Additional variables though likely explain differences in recurrence rates in patients with the same pre-LT HCC status. One of these variables is possibly immunosuppression (IS). Once recurrence takes place, management is highly heterogenous. Within the International Liver Transplantation Society Consensus Conference on Liver Transplant Oncology, working group 4 aim was to analyze the data regarding posttransplant management of recipients undergoing LT for HCC. Three areas of research were considered: (1) cancer prediction models and surveillance strategies; (2) tailored IS for cancer recipients; and (3) new adjuvant therapies for HCC recurrence. Following formulation of several questions, a literature search was undertaken with abstract review followed by article retrieval and full-data extraction. The grading of recommendations assessment, development and evaluation (GRADE) system was used for evidence rating incorporating strength of recommendation and quality of evidence.

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INTRODUCTION

Despite refinement of models, recurrence of hepatocellular carcinoma (HCC) following liver transplantation (LT) occurs in 6%–18% of patients transplanted for HCC. Recurrence is partially predictable and thus represents not only the loss of a potential donor resource, but also the added, and problematic challenge, of managing a presumably accelerated tumor progression in an immunocompromised host. Within a consensus conference led by the International Liver Transplantation Society on LT oncology 3 consensus papers, published in this issue of

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TABLE 1.

Prediction of hepatocellular carcinoma recurrence after liver transplantation

	Clinical features	Histological features	Immunological features	Background liver disease	Radiological features	Others
Pretransplant						
Parfitt et al[7]	AFP > 100 OKT3 monoclonal antibody	At LT histology Tumor grading Vascular invasion Microsatellites Giant / bizarre cells		Cryptogenic cirrhosis	Milan vs UCSF	
Decaens et al[8]		At pre-LT biopsy Tumor differentiation			At listing Size-and-number	
Guerrini et al[9]		At pre-LT biopsy Tumor grading			At listing Size-and-number	
Marsh et al[10]		At histology Tumor differentiation			At histology Size-and-number	
Agopian et al[11]	Maximum AFP Total cholesterol	At histology Tumor grading Vascular invasion No incidental tumor > 5 cm	Pre-LT NLR		Outside MC Radiol max tumor diameter	No pre-LT downstaging Y from LT
Sasaki et al[12]	Pre-LT AFP		Pre-LT NLR	Pre-LT MELD Na Underlying cause of cirrhosis	At histology Tumor burden score Milan criteria status	Y from LT History of LRT
Duvoux et al[13]	On listing AFP				On listing Size-and-number	
Mazzaferro et al[14]	AFP				At listing/histology Size-and-number	
Mehta et al[15]	At LT AFP	At histology mVI			At histology Sum of the largest viable tumor diameter and number of viable tumors	
Halazun et al[16]	Pre-LT AFP > 200	At histology Grading Vascular invasion	Pre-LT NLR ≥ 5		Pre-LT / At histology Size > 3 cm At histology Number > 3 cm	
Marsh et al[17]		At histology Vascular invasion Allelic loss of heterozygosity			At histology Size-and-number	Lobar distribution Pt gender
Posttransplant						
Sapisochin et al[18]	At recurrence AFP > 1000					At recurrence Curative intent Time of recurrence
Bodzin et al[6]	At recurrence AFP		Pre-LT NLR	At LT MELD > 23	At recurrence >3 nodules Maximum size Bone involvement	Time to recurrence Donor Na

AFP, alpha-fetoprotein; LRT, locoregional therapy; LT, liver transplantation; MC, Milan criteria; MELD, model for end stage liver disease; NLR, neutrophil-to-lymphocyte ratio; Pt, patient.

Transplantation,[1,2] were issued providing the evidence and best practices surrounding LT for oncological indications. The aim of our working group was to discuss and retrieve all the evidence regarding the best posttransplant approach in patients undergoing LT for HCC. Three areas of research were considered: (1) cancer prediction models and surveillance strategies; (2) tailored immunosuppression (IS) for cancer recipients; and (3) new adjuvant therapies for HCC recurrence. A key set of questions was considered, a literature search was undertaken, and recommendations were provided using the GRADE system incorporating strength of recommendation and quality of evidence.

CANCER RECURRENCE PREDICTION MODELS AND SURVEILLANCE STRATEGIES

LT for HCC is considered the best treatment option for patients with early-stage tumors (Barcelona clinic liver cancer A stage) selected according to Milan criteria (MC),[3] which dramatically reduced recurrence rates by implementing morphologic criteria for transplant eligibility. Straightforwardness and simplicity of the MC have made them a benchmark in this field. Yet, HCC recurs in a proportion of recipients who are within MC, while LT may provide cure for some patients who are beyond these criteria. Any expansion proposal carries an increased risk of HCC recurrence[4] and recurrence remains a major problem today, with rates of 15%–20% that are only partially predictable.[5,6]

Medical literature is scattered with cancer prediction models aimed at aiding morphological criteria to reduce recurrence (Table 1). These can be divided according to the driving mechanism of recurrence (pathological-, clinicopathological-, biochemical-, multiple-, and gene markers based-scores) and according to the time frame during which they can be applied (pre- and posttransplant scores).[19] Posttransplant models are useful not just to inform patient selection but to spot out patients who are at increased risk of recurrence and therefore deserve an increased surveillance or adjuvant therapy, if any were available.

In 2007, the first pathological score was created.[7] Recurrent HCC was more common (67% versus 12%; $P < 0.001$) in those who met University of California, San Francisco criteria because of a higher incidence of adverse histopathological features such as microvascular invasion, and in those with a preoperative alpha-fetoprotein (AFP) level > 1000 ng/mL. Pathological features impacting recurrence (independent of microvascular invasion) were nuclear grade, microsatellitosis, and giant/bizarre cells. By assigning a score to each of these variables, a nomogram was developed capable of stratifying patients into clinically relevant groups of low, intermediate, and high risk of recurrence. Another score built on pre-LT tumor differentiation at biopsy (n = 343) showed a higher accuracy than MC in predicting 5-year recurrence-free survival (RFS) with good reliability in an external validation cohort (n = 140) emphasizing that adding tumor differentiation to size-and-number improved HCC-LT selection.[8] A third predictive model of improved RFS-prediction (n = 130) included tumor grading (HR, 5.01; $P = 0.006$) and diameter (hazard ratio (HR), 1.46; $P = 0.045$).[9] Grade of differentiation and vascular involvement were also included in 2 further models. The first one[10] used an artificial neural network model including 5 risk factors (gender; tumor number, lobar distribution, and size; and extent of vascular invasion) to predict HCC recurrence within 1, 2, and 3 years. The second[11] proposed a novel clinicopathologic risk score and prognostic nomogram with an excellent ability to predict recurrence (C statistic = 0.85).

The hazard associated with liver transplantation for hepatocellular carcinoma score,[12] an individualized, preoperatively continuous risk metric model, based on tumor morphology and biology, background and liver function (MELD-sodium (MELD-Na), tumor burden score, AFT at LT, y from LT, cause of cirrhosis, neutrophil-to-lymphocyte ratio [NLR]-, prior locoregional therapy [LRT]-, and MC status) stratify the risk of mortality for patients within and outside MC more accurately and intuitively than the morphology only criteria.

Features of biological aggressiveness such as AFP have also been incorporated. A score based on AFP, tumor size-and-number was developed and further validated in different settings.[13] The model was found to be highly predictive of recurrence aiding in the selection of patients with HCC not meeting MC. The appropriate weight to AFP was also given by the Metroticket 2.0 study group[14] made by a training (n = 1018) and validation groups (n = 341). In the multivariable competing-risk regression analysis, the sum of tumor size-and-number and AFP levels were significantly associated with HCC-specific death ($P < 0.001$) and outperformed any other current transplant criteria for HCC. These items were included in an algorithm which has become an on-line calculator predicting 5-year survival and risk of pre-LT HCC-death adapting to variations in AFP and to tumor morphology induced by LRT (www.hcc-olt-metroticket.org/.)

The risk estimation of tumor recurrence after transplant score uses 3 variables independently associated with recurrence (microvascular invasion, AFP at LT, and the sum of the largest viable tumor diameter and number of viable tumors on explant).[15] It produces scores from 0 to 5 or higher that are associated with 5-year recurrence risks ranging from <3% to >75%.

In 2017, the model of recurrence after liver (MORAL) transplant score[16] was proposed combining morphological criteria (size > 3 cm) and biological markers including NLR ≥ 5 and AFP > 200 ng/mL. These features were independent predictors of worse post-LT recurrence in the multivariable analysis. Two different models originated from this data set. The pre-MORAL score applies to the pre-LT setting, delivering a risk of recurrence rate from 20% to 100%. The post-MORAL score uses 4 independent predictors of worse RFS available post-LT (grade 4 differentiation, vascular invasion, size > 3 cm, and number > 3). Both scores were superior to MC in predicting recurrence (C statistics of 0.82 and 0.87, compared with 0.63, respectively) and were statistically commixed to produce a combo-MORAL, with a high accuracy for prediction of recurrence (C statistic = 0.91). Tumor suppressor gene markers of allelic loss have also been advocated to provide further discriminative power combined with morphological, histological, and clinical features.[17]

Prognostication models can be applied also post-LT at the time of recurrence to weight the usefulness of particularly invasive surgical treatment approaches. In a model based on AFP at HCC recurrence (having 100 ng/mL as a cut off), time of recurrence (> or < 2 y from LT) and being or

not amenable to a curative-intent treatment, patients with a good prognostic score had a 5-year survival approaching 50%[18] In a large study,[6] predictors of mortality following HCC recurrence included nontumor factors (MELD at LT > 23, donor sodium, and pre-LT recipient NLR) together with time to recurrence, >3 recurrent nodules, maximum recurrence size, bone recurrence, and AFP at recurrence, demonstrating equally heterogeneous median survival times of 70.6, 12.2, and 3.4 months for the low, moderate, and high-risk groups, respectively ($P = 0.001$).

Considering the importance of a timely surgical intervention in case or recurrence, close surveillance after surgery is still highly recommended even though there are wide differences between centers in the time interval and the surveillance method. A recent multicenter study of 223 HCC recurrences found that increasing number of post-LT surveillance scans (3 surveillance scans within the first 24 months) was associated with receipt of potentially curative treatment (eg, surgery, ablation) and improved postrecurrence survival.[20] A reasonable suggestion is to perform abdominal and chest computed tomography every 6 months for 3 years after LT. Serial measurement of AFP is a useful adjunct for patients with elevated AFP levels pre-LT.[21]

Recommendations

- There is preliminary evidence that surveillance in HCC transplanted patients prolongs survival (moderate level of evidence and moderate recommendation).
- There is a need for a system to identify patients with a minimal risk of HCC recurrence in whom surveillance may not be recommended (moderate level of evidence and moderate recommendation).
- Given the lack of evidence regarding surveillance schedules, these can be based on prediction tools (low level of evidence and conditional recommendation).

TAILORED IMMUNOSUPPRESSION IN CANCER PATIENTS

Experimental and early observational clinical studies highlighted the interaction between IS and HCC recurrence. In vitro studies documented that calcineurin inhibitors (CNIs) promote tumor growth.[22] In addition, several retrospective studies demonstrated an association between CNI levels and HCC recurrence.[23-26] In one study, recurrence was highest (46%) when high CNI was present together with other clinical or histological risk factors (AFP > 50 ng/mL, macrovascular invasion, and G3–G4 grading). In patients with the same non-IS risk factors, but under low CNI, recurrence rate was only 15%.[25] In another study (n = 219), recurrence occurred in 9.4%, 22.1%, and 27.7% at 1, 3, and 5 years in those under high CNI exposure (mean concentration in the first post-LT mo > 10 ng/mL for tacrolimus or > 300 ng/mL for cyclosporine A) compared to 4.3%, 10.0%, and 14.7%, respectively in those under reduced CNI. In a multivariate analysis, high CNI exposure was independently associated with recurrence together with the main nodule diameter, microvascular invasion, and incidental macrovascular invasion.[26]

Interestingly, some HCC pathways are also the target of some IS agents, such as mammalian target of rapamycin (mTOR) inhibitors (mTORi).[27] Indeed, activation of the PI3K/AKT/mTOR pathway is common (50%–60%) in HCC and is correlated with poor HCC prognosis. Experimental evidence shows that mTORi have antiangiogenic and antiproliferative effects.[28] Retrospective studies have documented lower HCC recurrence and higher posttransplant survival in patients under mTORi IS compared to CNIs.[29-34] In the largest study (n = 2491 HCC and 12 167 non-HCC), sirolimus (SRL)-based IS was associated with improved 5-year survival in those with an HCC indication.[34] Five systematic reviews ± meta-analyses have been published comparing mTORi with CNI-based IS in HCC patients[35-39] (Table 2). A first systematic review and meta-analysis comparing SRL versus no SRL (n = 2950) showed that in comparison with SRL-free regimens, SRL-regimens improved overall survival at 1 (odd ratio [OR], 4.53; 95% confidence interval [CI], 2.31-8.89), 3 (OR, 1.97; 95% CI, 1.29-3.00), and 5 (OR, 2.47; 95% CI, 1.72-3.55) years and decreased tumor recurrence (OR, 0.42; 95% CI, 0.21-0.83).[35] In a second meta-analysis,[36] the recurrence rate was lower in the SRL group in comparison with CNIs (17.3%–38.7%). The 1-, 3-, and 5-year RFS was 93%–96%, 82%–86%, and 79%–80% for the SRL group, higher in comparison with CNIs (70%–78%, 64%–65%, and 54%–60%). The meta-analysis demonstrated lower recurrence (OR, 0.30; 95% CI, 0.16-0.55; $P < 0.001$), lower recurrence-related mortality (OR, 0.29; 95% CI, 0.12-0.70; $P = 0.005$), and lower overall mortality (OR, 0.35; 95% CI, 0.20-0.61; $P < 0.001$) for the SRL group. In the third systematic review, studies including everolimus (EVR)-treated patients were also included.[37] A total of 3666 HCC recipients from 42 studies met the inclusion criteria. Patients under CNIs developed recurrence more frequently than those under mTORi (13.8% versus 8%; $P < 0.001$), although patients on CNIs had a higher proportion of HCC within MC (74% versus 69%) and lower rates of microvascular invasion compared with mTORi-patients (22% versus 44%; $P < 0.05$). Patients on EVR had significantly lower recurrences compared with those on SRL or CNIs (4.1% versus 10.5% versus 13.8%, respectively; $P < 0.05$), but EVR-treated recipients had shorter follow-up period (13 versus 30 versus 43.2 mo, respectively) and had more frequently been transplanted for HCC within MC (84% versus 60.5% versus 74%, respectively; $P < 0.05$). In a 2019 study,[38] a total of 11 studies involving 7695 HCC patients were included. Compared with control group, SRL prolonged 1- (OR, 2.44; 95% CI, 1.66-3.59), 3- (OR, 1.67; 95% CI, 1.08-2.58), and 5-year (OR, 1.68; 95% CI, 1.21-2.33) overall survival, as well as 1-year (OR, 2.13; 95% CI, 1.19-3.81) RFS. SRL-patients had lower recurrence (OR, 0.60; 95% CI, 0.37-0.98), lower recurrence-related mortality (OR, 0.58; 95% CI, 0.42-0.81), and lower overall mortality (OR, 0.62; 95% CI, 0.44-0.89). In the most recent meta-analysis,[39] 23 studies were included (17 observational and 6 randomized trials), with 13 reporting on SRL and 10 on EVR. Meta-analysis demonstrated that compared with CNI controls, RFS was significantly increased with mTORi-based therapy at 1 (RR, 1.09; 95% CI, 1.01-1.18) and 3 (relative risk [RR], 1.1; 95% CI, 1.01-1.21) with a nonsignificant increase at 5 years (relative risk [RR], 1.15; 95% CI, 0.99-1.35). Overall survival was also improved at 1, 3, and 5 years. Recurrence rate was lower in the mTORi arm (RR, 0.67; 95% CI, 0.56-0.82) without differences based on the type of mTORi.

TABLE 2.

Systematic reviews ± metanalyses comparing mTORi and CNI-based IS in HCC-LT patients

Author et al (ref), no. of studies (type), no. of HCC cases	Inclusion criteria	HCC recurrence rate	Overall survival	Disease-free survival
Liang et al,[35] n = 5 (3 RS, 1 MCS, 1 CCS), 2950	Comparative studies	Lower in mTORi: (OR, 0.42; 95% CI, 0.21-0.83)	Higher in mTORi: 1 y (OR, 4.53; 95% CI, 2.31-8.89), 3 y (OR, 1.97; 95% CI, 1.29-3.00), and 5 y (OR, 2.47; 95% CI, 1.72-3.55)	Higher in mTORi: (OR, 2.41; 95% CI, 1.10-5.30; $P = 0.03$)
Menon et al,[36] n = 5 (3 RS, 2 PS), 474 (3 compare SRL-1979 vs CNI-189)	English language follow-up > 6 mo	Lower in mTORi: SRL (4.9%–12.9%) vs CNIs (17.3%–38.7%); OR, 0.30; 95% CI, 0.16-0.55; $P < 0.001$	Higher in mTORi: (94%–95%, 85%, and 80%) vs (79%–83%, 66%, and 59%–62%) at 1, 3, and 5 y; OR, 0.35; 95% CI, 0.20-0.61; $P < 0.001$	Higher in mTORi: (93%–96%, 82%–86%, and 79%–80%) vs (70%–78%, 64%–65%, and 54%–60%) at 1, 3, and 5 y; OR, 0.29; 95% CI, 0.12-0.70; $P = 0.005$
Cholongitas et al,[37] n = 42 (5 RCT, 9 PS, 28 RS); 3666 (CNI 3227) vs mTORi (439)	English language, January 2007–October 2013, comparative studies	Overall lower in mTORi: (448/3227, 13.8% vs 35/439, 8%; $P < 0.001$)[a,b,c]		
Zhang et al,[38] n = 11 (8 cohort studies, 1 MCS, 1 CCS, 1 RCT), 7873	Up to October 2017, no language restrictions, comparative studies	Lower in mTORi: (OR, 0.60; 95% CI, 0.37-0.98; $P = 0.04$)	Higher in mTORi: 1, 3, and 5 y: ORs, 2.44 (95% CI, 1.66-3.59; $P < 0.00001$); 1.67 (95% CI, 1.08-2.58; $P = 0.02$); and 1.68 (95% CI, 1.21-2.33; $P = 0.002$)	Higher in mTORi: 1 y (OR, 2.13; 95% CI, 1.19-3.81; $P = 0.01$), no differences at 3 y (OR, 1.18; 95% CI, 0.67-2.10; $P = 0.56$), or 5 y (OR, 1.50; 95% CI, 0.96-2.35; $P = 0.08$)
Grigg et al,[39] n = 23 (17 RS, 6 RCT), 6495	Up to December 2018, no language restrictions, comparative studies	Lower in mTORi: (RR, 0.67; 95% CI, 0.56-0.82)[d]	Higher in mTORi: 1 y (RR, 1.07; 95% CI, 1.02-1.12), 3 y (RR, 1.1; 95% CI, 1.02-1.19), and 5 y (RR, 1.18; 95% CI, 1.08-1.29)[d]	Higher in mTORi: 1 y (RR, 1.09; 95% CI, 1.01-1.18) and 3 y (RR, 1.1; 95% CI, 1.01-1.21), with a nonsignificant increase at 5 y (RR, 1.15; 95% CI, 0.99-1.35)[d,e]

[a]Patients on CNIs, compared with those on mTORi, had higher rates of HCC within Milan criteria before LT (1486/1999 [74%] vs 213/310 [69%], $P = 0.04$), lower rates of microvascular invasion (22% [202/953] vs 44% [64/146], $P < 0.001$), and had more frequently undergone LRT before LT (64.5% [809/1255] vs 51% [75/148], $P = 0.0004$).
[b]In RS/PS studies, recurrence was lower in mTORs (9.5% [31/324] vs 14.5% [439/3032], $P = 0.019$). In contrast, in RCT, the rates were similar (3.47% [4/115] vs 4.65% [9/195], $P = 0.77$).
[c]In MC patients, recurrence was lower in mTORi (3.8% [7/181] vs 9.2% [71/788], $P = 0.03$). In contrast, in the outside-MC, the rates were similar (29.5% [15/51] vs 29.2% [85/291], $P = 1.0$).
[d]No differences between SRL- vs EVR-based IS.
[e]For the outside MC subgroup, there was no significant difference in RFS between mTORis and CNIs at both 1 y (RR, 1.06; 95% CI, 0.94-1.19) and 3 y (RR, 0.95; 95% CI, 0.83-1.1).
CCS, case-control study; CNI, calcineurin inhibitor; EVR, everolimus; HCC, hepatocellular carcinoma; IS, immunosuppression; LRT, locoregional therapy; LT, liver transplant; MC, Milan criteria; MCS, matched cohort study; mTOR, mammalian target of rapamycin; mTORi, mTOR inhibitor; PS, prospective study; RCT, randomized controlled trial; RFS, recurrence-free survival; RS, retrospective cohort study; SRL, sirolimus.

However, there is no evidence that HCC is indeed sensitive to mTORi in the nontransplant setting even with doses that are higher than those used post-LT. Randomized controlled trials comparing EVR with placebo in sorafenib-exposed patients[40] and EVR plus sorafenib versus placebo plus sorafenib in sorafenib-naive patients[41] showed no improvement in overall survival. In the transplant setting, there is only 1 prospective randomized open-labeled International trial comparing SRL-containing versus mTORi-free IS in LT for HCC[42] and is also negative. In 3 years, 525 patients were randomized, 264 in the SRL-free arm (typically under CNI), and 261 in the SRL arm (on monotherapy or combination therapy with low doses of CNI). After 5-year follow-up, 149 (56.4%) and 138 (52.9%) remained under the same IS. RFS and overall survival did not differ between groups. In a planned analysis of RFS at yearly intervals, SRL group showed better outcomes at 3 years (HR, 0.7; 95% CI, 0.48-1.00). Similarly, survival was not statistically better in the SRL group at study end, but yearly analyses showed improvement out to 5 years (HR, 0.7; 95% CI, 0.49-1.00). Interestingly, subgroup analyses revealed that low-risk MC-patients rather than high-risk patients benefited most from SRL.

Of note, drug discontinuation due to adverse events has been reported to occur frequently with mTORi. Major side effects including dyslipidemia, hyperglycemia, and myelosuppression, are generally controlled by dose reduction. In contrast, less frequent adverse events such as nephrotoxicity, dermatological and mucosal side effects, and

interstitial pneumonitis are idiosyncratic reactions, typically unpredictable.[35-39,43]

In conclusion, there is accumulating evidence linking increased exposure to IS and carcinogenesis, particularly concerning CNIs, whereas exposure to mTORi may decrease this risk. However, only experimental and clinical retrospective data have confirmed this antineoplastic effect while the only prospective randomized trial has failed to confirm it.

Recommendations

- We suggest that initial target CNI trough levels in patients undergoing LT for HCC should be < 10 ng/mL for tacrolimus and < 300 ng/mL for cyclosporine A (low level of evidence and strong recommendation).
- Although retrospective data point towards a protective effect of mTORi, there is no evidence to recommend a specific type of IS in patients undergoing LT for HCC (moderate level of evidence and conditional recommendation).

NEW ADJUVANT THERAPIES FOR RECURRENCE OF HCC AFTER TRANSPLANTATION

Strategies to manage recurrence[44] are mainly based on retrospective studies, case series, and expert opinion. Future developments will be based on clinical studies performed in a nontransplant setting. Posttransplant recurrence can be divided in systemic and oligo-recurrence inside or outside the liver graft, with the lung and bone as the most common sites. Complete staging in case of posttransplant recurrence is needed to differentiate between disseminated or oligo-recurrence.

In case of recurrence, dosing and regimen of IS could be reconsidered, although no clinical studies support this approach. The same holds true for switching to an mTORi.[36,42,45] Depending on the general condition of patient, treatment with one of the multityrosine kinase inhibitors is advocated. The efficacy of sorafenib has been studied in 10 retrospective studies, mostly in combination with an mTORi. Complete or partial response rate was observed in a small fraction of patients, but stable disease was present in many leading to a survival benefit between 7.5 and 20 months compared to best supportive care.[46-49] A high proportion of patients need dose reduction (28.8%–90%) or discontinuation (4.1%–30%) due to toxicity of sorafenib. Most toxicities were grade 1 or 2. Other kinase inhibitors like lenvatinib, regorafenib, or cabozantinib have shown activity in the nontransplant setting[50-54] but their role post-LT still has to be determined. In a retrospective, multicenter, international study including regorafenib-treated LT patients having previously failed sorafenib (n = 28), all patients had at least 1 adverse event, the most common grade 3/4 being fatigue and dermatological reaction.[54] While no liver rejection was observed, plasma levels of IS drugs increased in 5.

Immunotherapy for HCC targeting immune checkpoints, programmed cell death protein-1 (PD-1), and cytotoxic T-lymphocyte-associated antigen-4 has been explored in a nontransplant setting. PD-1 blockers nivolumab and pembrolizumab have been validated in phase II trials with a 15%–20% response rate including complete responses, disease control in 64% of patients and a more favorable side effect profile compared with sorafenib.[55] In the setting of organ transplantation, however, immunotherapy checkpoint inhibitors may interfere with immune tolerance against the allograft by inhibition of regulatory T-cell subsets. Indeed, though experience with PD-1 blockers in LT is scarce, a risk of treatment-resistant allograft rejection has been reported.[56,57]

Management of oligo-recurrence by surgical resection is associated with survival benefit. More recent, the role of ablation, trans-arterial chemoembolization, and stereotactic body radiation have been explored in patients with recurrence.[44]

In conclusion, systemic or LRT is frequently used after LT for HCC recurrence. Based on retrospective studies, sorafenib with or without LRT is advocated with an expected survival and toxicity profile similar to the nontransplant situation. Future well-designed clinical studies with newer multikinase inhibitors are needed.

Recommendations

- Posttransplant recurrence should be surgically approached in a curative manner, whenever possible (moderate level of evidence and moderate recommendation).
- Based on the sorafenib as adjuvant treatment in the prevention of recurrence of hepatocellular carcinoma trial in resection setting, there is no recommendation for any adjuvant therapy to prevent recurrence (high level of evidence and strong recommendation).
- After recurrence, the recommendations for patient management do not differ to those applied before transplant (moderate level of evidence and moderate recommendation).

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