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REVIEW

Recurrent hepatocellular carcinoma after liver transplantation – an emerging clinical challenge

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Summary

In western countries, hepatocellular carcinoma (HCC) is a major reason for orthotopic liver transplantation (OLT) with estimated recurrence rates between 15% and 20%. This selective literature review addresses follow-up care after OLT in HCC and current treatment options. Recurrence prediction is based on pathological tumor stage, vascular invasion, serum alfafetoprotein levels, and histological differentiation, but further advances are expected by molecular profiling techniques. Lower levels of immunosuppressive agents are associated with a lower risk for HCC recurrence. Retrospective studies indicate that mammalian target of rapamycin (mTOR) inhibitors as immunosuppression reduce the risk of HCC recurrence. However, prospective studies supporting this potential advantage of mTOR inhibitors are still lacking, and higher rejection rates were reported for sirolimus after OLT in HCC. Prognosis is poor in recurrent HCC, a longer interval between OLT and recurrence and feasibility of surgical resection are associated with improved survival. Systemic treatment with sorafenib is the current standard of care in patients with advanced-stage HCC not suitable for locoregional therapy. After OLT, combination of an mTOR inhibitor with sorafenib is feasible and frequently used in clinical practice. As safety and efficacy data are still limited, close clinical monitoring is mandatory.

Introduction

The worldwide incidence of hepatocellular carcinoma (HCC) is rising and actually estimated to 750 000 new patients per year [1]. HCC patients with limited tumor size without macroscopic vascular invasion have a favorable outcome after orthotopic liver transplantation (OLT). The 5-year recurrence-free survival in this group of patients is over 80% [2,3]. In the absence of contraindications, OLT is, therefore, the preferred treatment in early stage HCC in many centers [4].

Because of the model of end stage liver disease-based allocation system supplemented by standard exceptions for early stage liver cancer, HCC has become a major indication for OLT in many western centers. For several reasons, the number of OLT as a result of HCC will likely increase further. As a consequence of the hepatitis C virus (HCV) epidemic, the incidence of HCV-related liver cirrhosis and liver cancer is rising in Western countries and Japan [5,6]. Moreover, obesity and nonalcoholic steatohepatitis have been identified as a risk factor of HCC in Western countries [7]. Given the proportion of obesity in Western populations, HCC as a result of nonalcoholic steatohepatitis is likely to increase. Surveillance programs are still not implemented in many regions, and there is a realistic chance to enhance the number of patients diagnosed with early stage HCC by promoting adequate surveillance in high-risk groups, e.g., in patients with chronic HCV infection. Moreover, expansion of the Milan criteria (Table 1) is continuously discussed because selected patients with larger tumors may archive similar survival rates after OLT as patients are fulfilling these criteria [3,8–11]. Because of the dramatic shortage of donor organs, expansion of transplant criteria associated with a

Table 1. Selection criteria for liver transplantation in patients with HCC.

Milan criteria [3]	1 tumor ≤5 cm or a maximum of 3 tumors each ≤3 cm
Up-to-seven criteria [8]	sum of maximal tumor diameter and number of tumor nodules ≤7
UCSF criteria [9]	1 tumor ≤6.5 cm or max. 3 tumor nodules each ≤4.5 cm and sum of tumor diameters ≤8 cm
Toronto criteria [10]	Any tumor size or number and no systemic symptoms as a result of HCC and histological-based exclusion of poorly differentiated HCC (beyond Milan tumors only)

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

substantial decrease in survival rates is currently not justified. A limitation of the Milan criteria is the dependence on imaging results. A discrepancy rate of 53% (30% falsely considered inside and 23% falsely outside the Milan criteria) comparing pretransplant imaging and histopathological staging of the liver explant has been reported [9].

Recurrence after liver transplantation will become a significant problem in the coming years, even with an anticipated recurrence rate below 20% [12]. Currently, no adjuvant treatment is established and treatment options after HCC recurrence are limited. This review summarizes current options and developments for the management of patients with HCC undergoing OLT based on a selective literature search. The PubMed database was screened independently for relevant publications with the search term ''liver transplantation HCC recurrence'' without limits by two authors (MWW, JT) of this review. Relevant articles published between January 2000 and January 2012 were supplemented with articles known to the authors and those identified by references. Articles not published in English language were not considered.

Risk factors for recurrence

Despite careful selection of patients for OLT, HCC recurrence remains a clinical meaningful problem [12]. In a recent study, HCC recurrence after OLT occurred in 16/60 (26.7%) patients between 4 and 58 months (median, 23 months). The median overall survival after recurrence was 10.5 months (range, 1–136 months) and only late recurrence and eligibility for surgery were positively correlated with survival [13]. Established predictors for HCC recurrence are tumor-specific factors as well as alphafetoprotein (AFP) levels before transplantation (Table 2). A meta-analysis on pretransplant risk factors for HCC recurrence showed significant correlations for the presence of vascular invasion, poor differentiation, tumor size >5 cm, and tumor stage outside the Milan criteria [14]. As vascular invasion and a tumor size >5 cm are included in a tumor stage considered exceeding the Milan criteria, the only risk factor identified within this meta-analysis for patients with a tumor stage within the Milan criteria was a moderate or poorly differentiated HCC. A score merged of combination of these criteria, however, was not prospectively evaluated. On the other hand, in a study of 95 patients with HCC undergoing OLT, HCC recurrence rates were significantly higher in patients who underwent a fine needle biopsy prior to transplantation in comparison to patients without a biopsy (31.8 vs. 5.9%, $P = 0.003$) [15]. Current diagnostic algorithms, e.g., the European Association for the Study of the Liver (EASL) criteria, allow noninvasive diagnosis of suspected HCC in patients with liver cirrhosis [16,17]. Biopsy is recommended only in case of inconsistent results, e.g., small nodules lacking a typical arterial-phase hypervascularization perfusion and/or a venous-phase washout signal.

Table 2. Established risk factors for HCC recurrence after liver transplantation.

Tumor-related risk factors	Immunosuppression-related risk factors
High AFP [10,50]	Level of immunosuppression [39]
Tumor grading [14,39]	mTOR- vs. mTOR inhibitor-free [47,50]
Tumor stage [13,14,39,50,91]	
Vascular invasion [13,14,50]	

AFP, alphafetoprotein; HCC, hepatocellular carcinoma.

Moreover, microvascular invasion and tumor stage were identified as major risk factors for HCC recurrence [13]. Of note, only 1 of 27 (4%) patients fulfilling the Milan criteria compared with 15 of 33 (45%) patients exceeding the Milan criteria developed recurrent HCC ($P < 0.001$). Most common metastasis sites were lung [4/16 (25%)], liver [4/16 (25%)], and bone [4/16 (25%)]. Nevertheless, overall 5-year survival rate in patients exceeding the Milan criteria was 65.6%, which highlights the value of liver transplantation for patients with HCC as well as the need for better markers for recurrence prediction [13]. Based on the dismissal outcome of patients with poorly differentiated HCC, the Toronto transplant group established the ''expanded Toronto criteria'' (Table 1), which have been developed for patients outside the Milan criteria. After exclusion of poorly differentiated HCC, the 5-survival rates of patients exceeding the Milan criteria and those fulfilling the Milan criteria showed no

difference, although the survival curves were apparently slightly higher for patients inside the Milan criteria [10].

All clinical staging systems are limited because the tumor biology in a given patient cannot be determined confidently, and therefore the individual prognosis at the time of the initial diagnosis remains uncertain [18–21]. According to the Barcelona Clinic Liver Cancer (BCLC) approach, resection is the treatment of choice in patients with limited tumor size and normal bilirubin levels as well as absence of portal hypertension [22]. In these patients, rescue OLT is feasible in case of recurrent or *de novo* liver cancer fulfilling the Milan criteria [23]. In contrast, in patients with (very) early stage HCC, but impaired liver function, OLT is recommended as primary treatment approach [24]. Repeated transarterial chemoembolization (TACE), as a bridging therapy for patients awaiting a liver transplantation with impaired liver function or resection in those patients without impaired liver function, might contribute to selection of patients with biologically less aggressive tumors and therefore to further reduction in HCC recurrence rates after OLT [25].

To overcome the weak correlation between tumor stage and biological behavior of HCC [18–21], molecular profiling by high-throughput technologies is currently investigated [26–28]. In a training set of 89 HCC patients with HCV-related liver cirrhosis, who were treated with liver transplantation or liver resection, three major micro RNA (miRNA) clusters were identified. Expression levels of three miRNAs representative for each cluster (miR-517a, miR-520g, miR-516-5p) were verified in a larger cohort ($n = 165$) of patients with different underlying liver disease. Especially, miR-517a promoted tumorigenesis and metastatic spread *in vivo*. Moreover, low expression of two other miRNAs (miR-26a, miR-26b) was correlated with impaired survival [26].

Sato *et al.* analyzed miRNA expression profiles in paired tumor and nontumor liver samples obtained from 73 patients, who underwent partial liver resection due to HCC mainly associated with chronic hepatitis B or C virus infection [27]. Both in tumor as well as in corresponding nontumor tissue, miRNAs associated with recurrence were found. Expression of certain tumor miRNAs was mainly negatively correlated with recurrence-free survival, suggesting a potential tumor-suppressor function. In contrast, expression of relevant miRNAs in corresponding nontumor tissue was positively associated with HCC recurrence, which may indicate a potential oncogenic function of these. Whether quantification of miRNA from nontumor samples may help to identify patients with chronic liver disease at risk for development of HCC prior has to be investigated in future prospective trials. Villanueva *et al.* recently reported the results of a comprehensive gene expression analysis in 287 HCC and 226 corresponding nontumor tissue liver samples from patients with liver cirrhosis who underwent partial liver resection for HCC. Different gene expression signatures were identified and correlated with early and overall HCC recurrence [28].

Chen *et al.* identified miRNA-203 as a potential prognostic marker for HCC recurrence after OLT [29]. Low expression of miRNA-203 in tumor tissue was found in patients with ($n = 16$) compared with high expression in patients without ($n = 50$) HCC recurrence after OLT ($P = 0.003$). Concordantly, high miRNA-203 expression was associated with better recurrence-free and overall survival ($P = 0.16$ and $P = 0.003$, respectively). Even in multivariate analysis, high miRNA-203 expression was an independent factor of better prognosis.

Recently, Barry *et al.* identified a set of 67 miRNAs in HCC obtained from explanted livers in 69 patients as a prognostic biomarker for HCC recurrence after OLT [30]. As multifocal HCC can be of different clonal origin, they applied a method to include miRNA profiles obtained from different tumor nodules. The biomarker was reported to distinct well between HCC recurrence and nonrecurrence within 3 years after OLT ($R^2 = 0.848$, area under the curve = 0.989). Clinically important, 9/12 (75%) patients who showed HCC recurrence despite a tumor stage within the Milan criteria as well as 8/11 (73%) patients without HCC recurrence despite a tumor stage outside the Milan criteria were identified correctly using the biomarker. Currently, prospective evaluation of this promising marker has to be performed.

Neovascularization leading to early arterial hyperperfusion is considered an essential step in HCC tumorigenesis [17,31], and the vascular endothelial growth factor (VEGF) likely plays an important role in neovascularization during HCC development in liver cirrhosis [32,33]. Moreover, increased VEGF serum levels have been correlated with HCC recurrence after resection [34]. Wu *et al.* investigated seven VEGF gene polymorphisms in 93 HCC patients treated with OLT [35]. The polymorphism rs3025035 was associated with HCC recurrence ($P = 0.003$), but none of the other six tested polymorphisms. However, even patients with a heterozygous rs3025035 status showed reduced recurrence-free survival (odds ratio 3.3; 95% confidence interval, 1.8–6.0; $P < 0.001$). Subsequent genome wide association studies may be helpful to identify further SNP's in other, e.g., European or African populations.

Taken together, molecular profiling is a promising but still cost intensive approach to predict HCC recurrence, and is currently still considered experimental. Future prospective evaluation is needed before the implementation into routine practice for selection of OLT candidates.

Strategies to prevent recurrence after OLT

Strategies to prevent HCC recurrence after OLT may be distinguished in strategies based on immunosuppression (e.g., use of immunosuppressive drugs with antiproliferative activity, level of immunosuppression) and more specific adjuvant therapies.

Influence of immunosuppressive drugs on HCC recurrence

The immune system is substantially involved in the control of malignant cells. As early as 2 years after solid organ transplantation, the cancer risk increases and the overall cancer incidence remains doubled thereafter [36]. Moreover, the growth rate in recurrent HCC after OLT is accelerated, likely as a result of immunosuppression [37].

Tacrolimus-based immunosuppression is now the most commonly used regimen in OLT patients. Compared to cyclosporine, the use of tacrolimus results in improved survival and prevention of acute rejection [38]. Higher plasma levels of both tacrolimus and cyclosporine are associated with higher HCC recurrence rates [39]. Therefore, reduction in immunosuppression as far as possible seems a reasonable approach to reduce the risk of HCC recurrence. This is emphasized to be a recent study showing that a better immune status, estimated by values of CD(+) T cells produced adenosine triphosphate levels, was associated with better disease-free survival [40].

In addition, the choice of the immunosuppressive drug may influence the cancer risk after solid organ transplantation. Inhibitors of the mammalian target of rapamycin (mTOR), which act both as immunosuppressant as well as antineoplastic agent, might reduce HCC recurrence rates [41,42]. Currently, no mTOR inhibitor is approved by the European Medicine Agency (EMA) for organ rejection after OLT. Nevertheless, feasibility of sirolimus-based immunosuppression has been shown [13,43–45], and retrospective studies suggest that sirolimus-based immunosuppression may be associated with delayed tumor recurrence compared with tacrolimus-based regimens [46–48]. Whether mTOR inhibitors are beneficial after OLT due to HCC was further studied retrospectively in 97 patients receiving a calcineurin inhibitor with or without sirolimus [49]. HCC recurrence rate was apparently higher in the mTOR inhibitor-free group (9/52, 17%) than in the mTOR inhibitor group (3/45, 7%). Most importantly, survival at 1 and 5 year(s) after OLT was improved in the mTOR inhibitor group (95.5% and 80% compared with 83% and 62%, respectively). Another retrospective study including 2491 patients with HCC and 12 167 patients without HCC investigated the influence of immunosuppressive regimens on 5-year survival rates after OLT [44]. In a multivariate analysis, survival was improved in HCC patients being treated with silorimus for immunosuppression compared with HCC patients not being treated with sirolimus (83% vs. 69%). Zhou *et al.* investigated whether HCC recurrence was different in 73 patients with respect to sirolimus ($n = 27$) vs. tacrolimus ($n = 46$)-based immunosuppression [48]. Mean overall and mean disease-free survival were 594 ± 35 days and 519 ± 43 days in sirolimus treated patients compared with 480 ± 42 days and 477 ± 48 days in tacrolimus treated patients ($P = 0.011$ and $P = 0.234$, respectively). The so far largest prospective trial analyzed 106 patients receiving tacrolimus and mycophenolate mofetil compared with 121 patients who received sirolimus as rejection prophylaxis after OLT [50]. Both, HCC recurrence-free survival ($P = 0.0003$) and overall survival rates at 1 (94% vs. 79%), 3 (85% vs. 66%), and 5 (80% vs. 59%, $P = 0.001$) years after OLT were significantly higher in sirolimus-treated patients. The ongoing, prospective SiLVER trial was designed to answer whether sirolimus-based immunosuppression is superior to mTOR inhibitor-free immunosuppression in patients undergoing liver transplantation for HCC [51]. The primary objective of this phase III trial (estimated patient enrollment, $n = 510$) is HCC recurrence-free survival 5 years after liver transplantation. Final study completion is estimated in March 2014. Recently, higher rates of acute rejection ($P = 0.02$) and treatment discontinuations ($P < 0.001$) were reported within another clinical trial in patients with conversion to sirolimus in contrast to those with maintained calcineurin inhibitor-based immunosuppression therapy at week 52. This study failed to meet the primary safety end point of noninferiority of cumulative rate of graft loss or death at 1 year (6.6% vs. 5.6% in the patients receiving sirolimus and patients receiving calcineurin inhibitors, respectively) [52]. Safety, tolerance, and efficacy of mTOR inhibitors in patients after OLT must be further evaluated in randomized clinical trials.

Adjuvant strategies for prevention of HCC recurrence

The sensitivity of advanced HCC to cytotoxic, antihormonal or immunomodulating treatment is low. One study comparing adjuvant chemotherapy with fluorouracil, doxorubicin, and cisplatin in 25 patients with OLT as a result of HCC with a historic control group suggested improved survival [53]. More recent studies using 5-fluorouracil/carboplatin, cisplatin/adriamycin, or doxorubicin, however, failed to show any efficacy of adjuvant chemotherapy after OLT [54–56]. A further study reported a 3-year survival benefit in patients exceeding the Milan criteria when treated with oxaliplatin, 5-fluorouracil, and leucovorin after liver transplantation (73.3% vs. 62.1%) [57].

In this open-label study, a bias could not be excluded and therefore the results must be interpreted with caution. In summary, conflicting data about adjuvant chemotherapy in patients with HCC and liver transplantation have been reported and therefore adjuvant chemotherapy cannot be recommended in this clinical setting.

Adjuvant oncolytic adenoviral therapy is an experimental treatment modality in HCC patients treated with OLT. Adenovirus-mediated delivery of herpes simplex virus thymidine kinase, which mediates sensitivity to antiviral drugs like ganciclovir, followed by administration of ganciclovir, has been evaluated in a cohort of 45 patients with HCC not fulfilling the Milan criteria, but treated with OLT [58]. After a median follow-up of 26 months (range, 2–50 months), 1 and 2 year(s) recurrence-free survival in patients without adjuvant oncolytic adenoviral therapy was 18.2% (4/22) and 9.1% (2/22), respectively, compared with 60.9% (14/23) and 43.5% (10/23) in patients with adjuvant oncolytic adenoviral therapy ($P = 0.001$). Furthermore, the 1- and 2-year overall survival was 40.9% (9/22) and 22.7% (5/22) in patients without compared with 73.9% (17/23) and 69.6% (16/23) of patients with adjuvant oncolytic adenoviral therapy ($P = 0.001$). In a multivariate analysis, only vascular invasion was identified in this cohort as a predictor of survival ($P = 0.002$) and recurrence ($P < 0.0001$), respectively. All patients with vascular invasion relapsed, but recurrence was delayed in patients with adjuvant treatment. Overall survival within this study was poor, most likely because only patients exceeding the Milan criteria were transplanted. Despite this limitation, this study serves as a proof-of principle for adjuvant oncolytic adenoviral therapy for HCC patients treated with OLT.

The heparanase inhibitor PI-88 has shown preliminary efficacy as adjuvant therapy for patients following curative HCC resection in a phase II study [59]. Moreover, different other agents including vitamin A and vitamin K2 analogues have been associated with improvement of disease-free survival as adjuvant treatment after partial liver resection or local ablation of HCC nodules [60]. Detailed reviews of (neo-)adjuvant treatment in HCC in patients without liver transplantation have been published previously [61,62], and may be cross-referenced as this topic is beyond the scope of this article. In patients with HCV-associated HCC, adjuvant treatment with interferon-alfa might reduce the risk of HCC recurrence and therefore improve the overall survival [63,64]. However, there is no consensus on the benefit of adjuvant interferon-alfa treatment after curative resection and especially after OLT.

Sorafenib, a multi-tyrosine kinase and angiogenesis inhibitor, which is used in advanced HCC as systemic treatment has been shown to reduce the HCC recurrence rate after surgical resection in a mouse model [65]. Currently, this hypothesis is investigated in an ongoing phase III trial as adjuvant treatment of HCC after surgery or local ablative therapy. Data from this trial are awaited not until 2014/2015. The principle feasibility and safety of such an adjuvant treatment with sorafenib has already been shown in a small cohort of eight liver transplant patients with high-recurrence risk [66]. In conclusion, there are currently no reliable data justifying adjuvant treatment after OLT in patients with HCC.

Treatment of recurrent HCC after OLT

In principal, all treatment options currently available for advanced HCC are also potentially feasible after OLT. Treatments include resection, ablation, transarterial embolization or radioembolization, and systemic treatment with sorafenib. Nevertheless, specific conditions after OLT have to be taken into consideration: influence of immunosuppression to wound healing, anatomic characteristics of vascular anastomoses, risk of stenosis of the hepatic artery by transarterial techniques, and potential pharmacological interactions between antineoplastic and immunosuppressive drugs.

Surgical and ablative options

Resection or radiofrequency ablation of HCC metastases can successfully be performed in some patients [67]. The ability for surgical treatment and a late onset (> 24 months) of recurrence are factors associated with long-term survival [13]. It seems reasonable that resection of HCC metastases after OLT is meaningful in patients with limited metastatic sites and late onset, as early HCC recurrence is associated with a poor prognosis. In one study, the median time-to-recurrence was 23.4 months in patients fulfilling the Milan criteria ($n = 182$) [67]. Surgical resection could be performed in 11/23 (48%) patients, and everolimus in combination with sorafenib was given to three patients after resection. Survival after HCC recurrence was 32.3 ± 21.5 months vs. 11.9 ± 6.9 months in patients with or without surgery, respectively ($P = 0.006$).

Transarterial chemoembolization

Transarterial chemoembolization (TACE) is often used as bridging therapy in patients awaiting liver transplantation. Consecutively, alterations of the hepatic artery may be observed increasingly with repeated TACE cycles. As stenosis or embolism of the arterial anastomosis is a typical complication within the first weeks after OLT, TACE after OLT seems more risky, especially in patients with repeated TACE cycles before OLT. Despite these concerns, successful TACE treatment of recurrent HCC after OLT

has been reported [68,69]. In the later small cohort study using lobaplatin and lipiodol ($n = 14$), significantly improved survival was shown compared with a matched control group not receiving TACE [69]. Despite a partial response rate of 57%, development of new lesions was comparable between patients treated with TACE (86%) and those from the matched control group (93%). In a further cohort study of 28 patients with recurrent HCC after living donor liver transplantation the 1-, 3-, and 5-year survival rates after treatment with repeated TACE were 47.9%, 6.0%, and 0%, respectively [68]. Intrahepatic and extrahepatic metastasis were reported in the majority of patients indicating that HCC recurrence after OLT is, in most cases, a metastatic disease, which is an argument for systemic rather than local treatment.

Radioembolization and brachytherapy

In principle, HCC is sensitive to radiation therapy, but limitations of external radiation therapy arise from the limited radiation tolerance dose of the liver. In contrast, selective intra-arterial radioembolization therapy is an option in patients with intermediate and advanced-stage HCC [70]. Zhang *et al.* investigated computed tomography-guided 125-iridium brachytherapy in 10 patients with predominantly lung metastasis of HCC recurrence after OLT [71]. In addition to a local control rate of 84% and 73% after 6 and 24 months, respectively, 8/10 (80%) patients were still alive after the end of follow-up after 44 months, whereas two patients died after 15 and 29 months, respectively.

Immunosuppression

Currently, sirolimus and everolimus are approved mTOR inhibitors used in patients after solid organ transplantation. A major reason for the preferred use is the reduced incidence of *de novo* malignancy, mainly skin cancer, compared with non-mTOR containing immunosuppressive regimens in organ transplant recipients [72]. Moreover, the PI3K/Akt/mTOR pathway is a key regulator of cellular proliferation and angiogenesis and has emerged as a contributor to hepatocarcinogenesis [73,74]. Therefore, the mTOR inhibitor everolimus is currently investigated in clinical trials in patients with HCC [75,76]. However, all these studies exclude patients after solid organ transplantation and are using higher, antiproliferative, doses of mTOR inhibitors, e.g., for everolimus 7.5–10 mg once daily. Given the overall poor prognosis of HCC recurrence and the limited systemic treatment options, switching to an immunosuppressive agent with intrinsic antiproliferative capability seems attractive and obvious possibility [77].

Sorafenib

Sorafenib is a multi-tyrosine kinase and angiogenesis inhibitor with activity against VEGFR2, PDGFR, c-Kit receptors, b-RAF, and p38, signal transduction pathways, which are involved in the HCC pathogenesis [78]. In patients with advanced HCC and compensated liver cirrhosis (Child-Pugh A), sorafenib has been shown to improve survival by approximately 3 months [79]. In the recent past, several groups have reported their retrospective experience with sorafenib, in most cases in combination with an mTOR-based immunosuppression [67,80–89]. Currently, the largest evidence for the combination of an mTOR inhibitor with sorafenib comes from a cohort study of 26 patients with HCC recurrence after OLT not suitable for surgical resection or locoregional treatment [89]. Of importance, patients were switched to an mTOR-based immunosupression (70% everolimus and 30% sirolimus) first and thereafter sorafenib was started after a median time of 1.1 (in case of everolimus) to 1.4 (in case of sirolimus) months. Ten of 26 patients started sorafenib with 800 mg per day, whereas 16 patients started with 400 mg per day. In this retrospective Spanish cohort study, the median time-to-progression was 6.8 months, while the overall survival was 19.3 months. The daily doses of either sirolimus or everolimus ranged between 1.0 and 4.0 mg (mean 2.6 mg/day for sirolimus and 2.2 mg/day for everolimus). Noteworthy, a phase I study in patients with HCC found that the mean tolerable dose of everolimus in combination with sorafenib 400 mg twice per day was only 2.5 mg/day [90]. Whether the immunosuppressive dose of an mTOR inhibitor is effective for tumor control remains to be shown in prospective clinical trials.

Hand-foot-skin reactions seem to be more pronounced in transplant patients, often leading to dose reductions [84,87]. Of note, a single case of severe acute hepatitis after sorafenib in a patient after liver transplantation has been reported [91]. Based on the current experience, adverse events were reported more often in transplant than in nontransplant HCC patients treated with sorafenib. Therefore, awareness of potential adverse effects and close monitoring of liver, renal, and bone marrow function as well as plasma levels of immunosuppressive drugs are mandatory.

Conclusions

Currently, the risk of HCC recurrence after OLT is predicted by clinical parameters and no adjuvant treatment is available. Novel molecular profiling techniques might further improve the prediction of the recurrence risk. Switching to an mTOR inhibitor-based immunosuppres-

sive regimen may be considered, but no prospective data are available that HCC recurrence is delayed by mTOR inhibitors. Moreover, mTOR inhibitors are currently not approved for organ rejection after OLT and the ideal time point to switch to an mTOR inhibitor-based immunosuppression is unknown. The most effective treatment of recurrent HCC after OLT is surgery. Treatment of recurrent HCC after OLT with sorafenib – either with or without an mTOR inhibitor as immunosuppressive treatment – seems feasible, but should be initiated under close monitoring because of potential severe side effects.

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