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Pilot study: Rapamycin in advanced hepatocellular carcinoma

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Key words: Hepatocellular carcinoma (HCC), rapamycin

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Abstract

Introduction: The PI3K/Akt/mTOR signal pathway is involved in hepatocarcinogenesis. Rapamycin (= Sirolimus), a specific mTOR inhibitor, leads to G(1) arrest of many malignant cell lines, and currently analogs of rapamycin are being investigated as a cancer chemotherapeutic adjuvant.

Aim: To study the toxicity and tolerability of rapamycin therapy in patients with advanced hepatocellular carcinoma (HCC).

Methods: Between June 2005 and February 2007 patients with advanced HCC, not eligible for any established therapy, were included in the study.

Results: 18 patients (f/m: 5/13) with compensated liver cirrhosis (Child A n= 11, Child B n= 5, Child C n=2) and histologically proven HCC were included in this study. According to the BCLC staging system most of the patients enrolled had an advanced HCC: BCLC stage B: n=2, BCLC stage C: n=14, BCLC stage D: n=2. Overall, therapy with rapamycin was well tolerated. Most common toxicities were thrombocytopenia and anemia. We did not observe any partial or complete tumor response. At 3 months two patients had stable disease, at 6 months all patients had progressed. The median overall survival was 5.27 months, median time to progression was 3 months. Conclusion: Rapamycin is well tolerated in patients with advanced HCC but only minimally effective.

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Introduction

Hepatocellular carcinoma (HCC) is a tumor of high prevalence worldwide and shows an increasing incidence in the western world. More than 90% of all Hepatocellular carcinoma develop in a cirrhotic liver. Known major risk factors for the development of liver cirrhosis and Hepatocellular carcinoma are chronic hepatitis B or hepatitis C, alcoholic liver cirrhosis or genetic hemochromatosis. The incidence rate of HCC in patients with underlying liver cirrhosis is approximately 3 to 4%[1].

Therapeutic options depend on the stage of underlying liver cirrhosis, on the number and diameter of tumor nodules and the performance status; these factors are combined in the BCLC [2] staging system. Liver transplantation and liver resection are potentially curative treatment options which were offered patients in BCLC stage A (Child-Pugh stage A, 1 nodule <5cm or 3 nodules < 3cm). Also local ablative treatment options (PEI, RFA) are potentially curative treatment options which were used in this group of patients. However, many HCC patients present with a BCLC stage B (Child-Pugh stage A or B, multinodular) or BCLC stage C (Child-Pugh stage A or B, multinodular, portal invasion, N1, M1; without potential curative treatment options). Transarterial chemoembolisation (TACE) for BCLC stage B or treatment with the vascular endothelial growth factor inhibitor Sorafenib for BCLC stage C are offered to these groups of patients and have been shown to prolong survival [3 4 5 6 7 8]. Sorafenib, a multikinase inhibitor, represents a breakthrough in the management of advanced hepatocellular carcinoma and shows a significantly better survival compared to placebo. Nevertheless, there is need for new therapeutic agents for those patients

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A recently discussed new treatment option is Rapamycin (= Sirolimus), a specific mTOR inhibitor („mammalian target of rapamycin“). Rapamycin is inhibiting the PI3K/Akt/mTOR signal pathway which is involved in multiple cellular functions including proliferation, differentiation, tumorgenesis, and apoptosis. Rapamycin, the naturally occurring inhibitor of mTOR and a number of recently developed rapamycin analogues inhibit the growth of cell lines derived from multiple tumor types in vitro, and tumor models in vivo., This specific mTOR inhibitor could lead to G(1) arrest of many malignant cell lines, and currently analogs of rapamycin are being investigated as a cancer chemotherapeutic adjuvant [9 10 11]. Rapamycin, isolated from Streptomyces hygroscopicus, is a Macrolid-antibiotic with antibacteriel, antifungal and immunosuppressive effects [12 13 14] and can inhibit mTOR through association with its intracellular receptor FKBP12. The FKBP12-rapamycin complex binds directly to the FKBP12-Rapamycin Binding (FRB) domain of mTOR. The inhibition of mTOR by Rapamycin causes a dephosphorylation and inactivation of some ribosomal proteins and leads to a reduction of synthesis of components of the translation process [15 16]. This is followed by an arrest of the G1-phase of cell cycle which causes immunosupression but also antitumoral effects.

Proteins regulating the mammalian target of rapamycin (mTOR) are overexpressed or mutated in cancer. Results from clinical trials indicate that rapamycin and its analogues may be useful for the treatment of subsets of certain types of cancer [17 18]. Therefore, in this pilot study we studied the toxicity and tolerability of rapamycin in patients with liver cirrhosis and hepatocellular carcinoma.

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METHODS

PATIENTS

A total of 18 patients were included into the study between June 2005 and February 2007. All patients were recruited at the Department of Gastroenterology and Hepatology at the Medical University of Vienna. Most of our patients were in Child B, only two were in Child C stage. Liver cirrhosis and its complications were managed according to state of the art protocols. The demographic data and baseline clinical characteristics are given in Table 1. Liver cirrhosis was diagnosed either by histology or by the typical combination of laboratory tests, clinical and gastroscopic findings and typical signs of liver cirrhosis in CT or ultrasound. Diagnosis of hepatocellular carcinoma was done according to the criteria of EASL [19] and AASLD [20].

Patients with histologically confirmed HCC were eligible if they were 19-85 years of age and were no candidates for liver transplantation, tumor resection, a local ablative therapy (kryotherapy, ethanol instillation, radio frequency ablation) or chemoembolization (TACE). One patient was switched due to progression of the HCC from TACE to Rapamycin. To be eligible for the study the estimated life expectancy had to be more than 3 months. Tumors had to be measurable objectively with CT-scan.

DEFINITION OF TUMOR PROGRESSION

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Tumor progression was judged during the study by comparing tumor diameters during follow up examinations against the measurements obtained at baseline. We used the RECIST [21 22] and EASL [19] response criteria for evaluation of progression free survival

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FOLLOW UP

Routine multislice CT and ultrasound were performed every three months until death of the patient. Physical examination, serum chemistry, blood cell counts and AFP determinations and Rapamycin plasma levels were done monthly.

TREATMENT MODALITIES

Rapamycin was administered orally twice daily. The target plasma level was 4 to 8 ng/ml. The planned duration of the study was 6 months. Toxicity assessments were based on reports of adverse events and results of scheduled physical examinations, vital sign measurements and clinical laboratory tests.

STATISTICAL ANALYSIS

Chi² test was used to compare proportions and Mann Whitney U tests to compare median values between groups. Survival times and progression free survival were estimated using the Kaplan-Meier method and the differences were tested with the log-rank test. Analysis was performed with Statistica (StatSoft, Inc. (2004). STATISTICA (data analysis software system), version 6. www.statsoft.com).

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Results

PATIENT CHARACTERISTICS

18 patients (female: 5, male: 13) with compensated liver cirrhosis (Child A n= 11, Child B n= 5, Child C n=2) and histologically proven HCC (G1 n=1, G2 n=14, G3 n=3) were included in this study. (Table 1)

According to the BCLC staging system most of the patients enrolled had advanced hepatocellular carcinoma: BCLC stage B: n=2, BCLC stage C: n=14, BCLC stage D: n=2.

TREATMENT TOXICITY AND TOLERABILITY

Overall, therapy with rapamycin was well tolerated. We did not observe severe infectious complications. Only 2 spontaneous bacterial peritonitis (SBP) were seen in the 18 patients. Most common laboratory abnormalities were thrombocytopenia and anemia, most often already present at baseline. Neither dose reduction nor termination of treatment was necessary due to severe toxicity.

TUMOR RESPONSE

We did not observe any partial or complete tumor response. At 3 months two patients had stable disease, at 6 months all patients had progressed.

TIME TO PROGRESSION

The median time to progression was 3.0 months. (Figure 2) The shortest time to progression was 1.2 months, the longest time to progression was 6.7 months.

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SURVIVAL

The median overall survival was 5.27 months. 6 patients died before the first assessment of tumor progression at 3 months, 5 further patients between the first CT assessment at 3 months and the end of the study at 6 months. 7 patients lived longer than 6 months. However, 3 of those died within one month after end of the study due to progression of disease. The remaining 4 patients, all having progressive disease, were switched to other treatments (3 patients to Sandostatin LAR, 1 patient to Sorafenib). They lived for 12, 16, 19 and 28 months respectively.

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Discussion

In this pilot study 18 patients with compensated liver cirrhosis and histologically proven advanced HCC were treated with Rapamycin, a specific mTOR inhibitor. At 3 months two patients had stable disease, at 6 months all patients had progressed. Our results showed that Rapamycin was well tolerated but was only minimally effective in patients with liver cirrhosis and advanced stage hepatocellular carcinoma.

Although all our patients had liver cirrhosis treatment with Rapamycin resulted in few side effects. No dose reduction due to intolerable side effects was necessary even in patients with Child B liver cirrhosis. We observed only two cases of SBP which were successfully treated with antibiotics despite continuous treatment with Rapamycin. No clear connection to Rapamycin treatment was evident in those patients. In general, in patients with liver cirrhosis and advanced HCC Rapamycin was well tolerated.

We treated our patients between 2005 and 2007 before Sorafenib was registered for treatment of HCC. At present Sorafenib is recommended in patients with advanced HCC and any new treatment should be evaluated against that standard. Sorafenib, a drug which has been proven to prolong survival of patients with advanced HCC in the SHARP trial [6], did not induce complete response in a single patient and only 2% of all patients had a partial response. We saw a similar picture: although we did not observe any partial or complete tumor response at 3 months two patients had stable disease. In the SHARP trial the median time to radiologic progression was only 5.5 months in the sorafenib group. Similarly, under

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Rapamycin treatment all patients had progressed at 6.7 months, the median time to progression was 3.0 months. In general, the limited tumor response and the progression of tumor size do not indicate ineffectiveness of the treatment with Rapamycin, there is considerable discussion whether the EASL and RECIST criteria used to document tumor progression are the best tools to judge the effectiveness of an anti-tumor drug. Focusing on objective tumor shrinkage does not take into account the possibility of other potential beneficial effects of a drug on survival. Median overall survival time was 10.7 months in the sorafenib group in the SHARP trial but only 5.27 months in our patients treated with Rapamycin. Our one year survival rate was 22%. The expected one year survival rate of patients with BCLC stage C without therapy according to BCLC staging classification would have been 29% [2] which is not different from our patients actively treated with Rapamycin. However, 97% of the patients with advanced hepatocellular carcinoma included in the SHARP trial were rated as Child stage A at baseline, reflecting a well-preserved liver function. On the other hand 38.9% of our patients treated with Rapamycin were classified as Child stages B or C. Therefore patients included in our trial had worse baseline characteristics and were not directly comparable to the patients included in the SHARP trial. Therefore the effectiveness of Rapamycin can only be evaluated in comparison to a placebo group. New, randomized controlled studies are needed to investigate the effectiveness of Rapamycin or other mTOR inhibitors in patients with hepatocellular carcinoma.

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Rapamycin provokes antineoplastic and immunosuppressive effects. Organ transplant recipients treated with mTOR inhibitors have a reduced incidence of de novo posttransplant malignancies. Therefore, the use of Rapamycin in recipients with a high cancer risk like older patients, recipients with a personal history of cancer or high familial cancer risk, could be claimed. Immunosuppressive therapy after liver transplantation might contribute to

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recurrence and metastasis of hepatocellular carcinoma. mTOR inhibitors as immunosuppressive agents are an excellent treatment alternative in that situation with data showing an excellent survival and disease free intervals in those patients [23 24 25]. A recently published study based on the Scientific Registry of Transplant Recipients (SRTR) including 2,491 adult recipients of isolated liver transplantation for HCC and 12,167 for non-HCC diagnoses revealed that sirolimus based immunosuppression compared to calcineurin inhibitors has unique posttransplant effects on patients with HCC that lead to improved survival[26].

The primary usage of mTOR inhibitors as an anti tumor agent in patients with a malignancy but without organ transplantation is controversially discussed [27]. However, recent studies show that the mTOR pathway has an important role in the pathogenesis of HCC. Villanueva et al. demonstrated that an aberrant mTOR signaling was present in half of the cases [17]. The authors showed that the blockage of mTOR signaling with Rapamycin in vitro and in xenograft models decelerated tumor growth and increased survival. These findings are the rationale for targeting the mTOR pathway in clinical trials in patients with HCC.

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In summary, Rapamycin is well tolerated in patients with advanced hepatocellular carcinoma but only minimally effective.

STATEMENT OF INTERESTS:

No financial support was received for this study.

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Figure 1

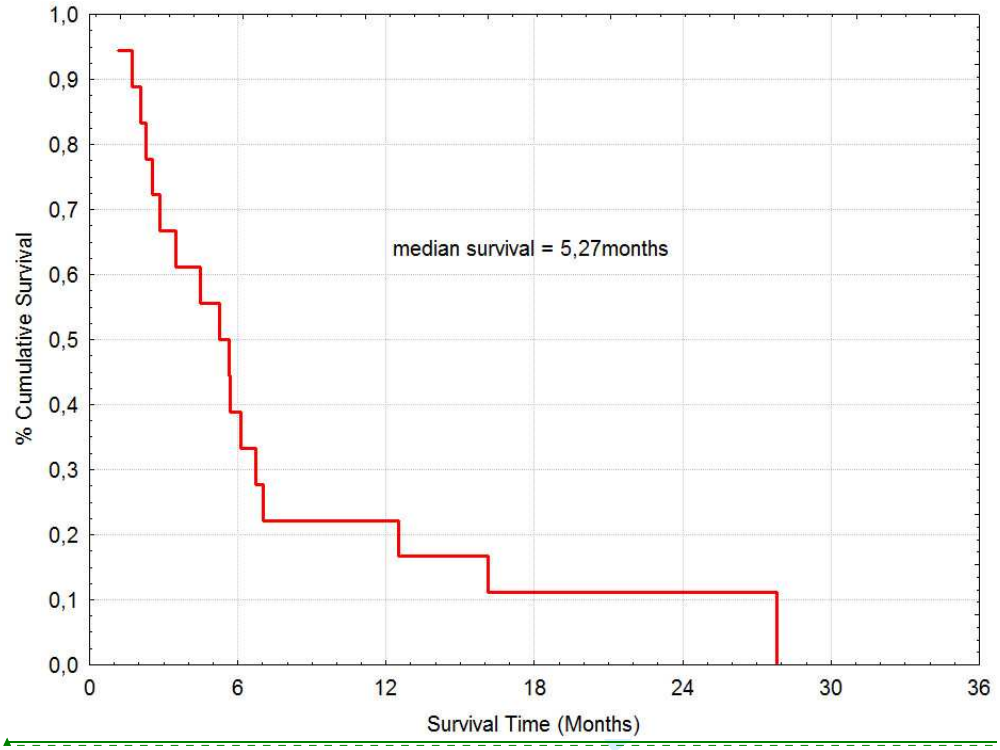

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Figure 2

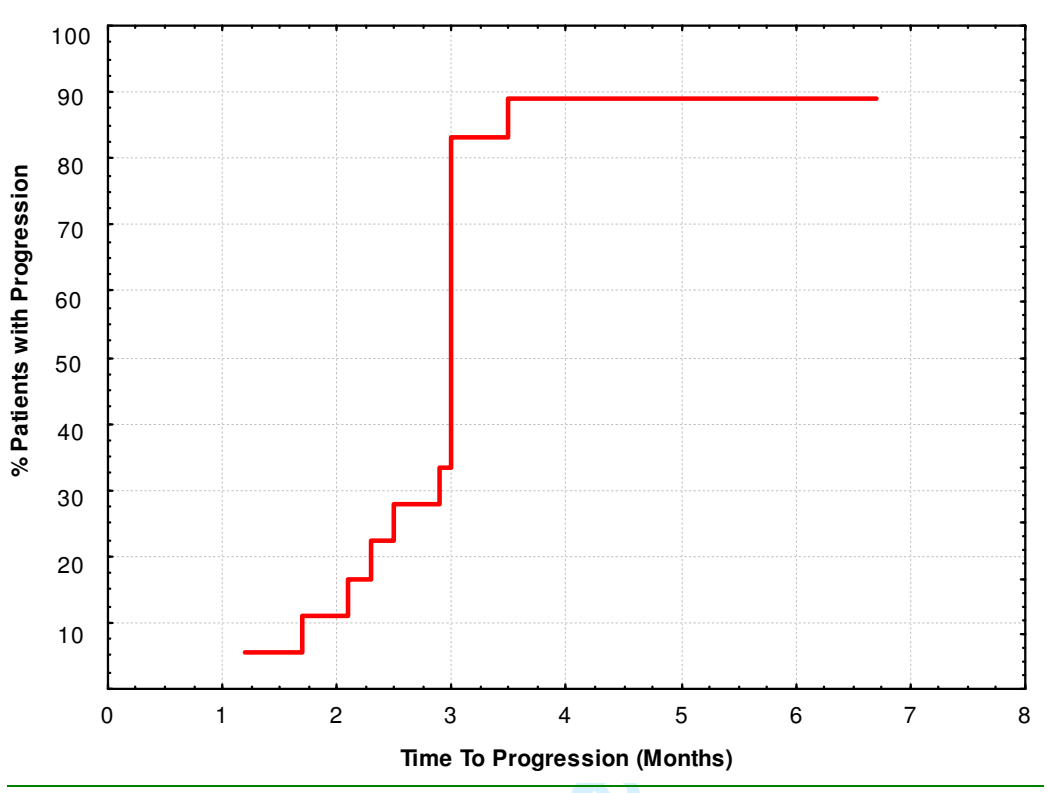

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Table 1, Patient characteristics, baseline parameters

		overall
		number (percentage)
Number		18
Sex		
	male	13 (72.2%)
	female	5 (27.8%)
Median age (range)		64.2 (46.5 - 80.9)
Liver cirrhosis		
	Child A	11 (61.1%)
	Child B	5 (27.8%)
	Child C	2 (11.1%)
BCLC		
	Stage A	0
	Stage B	2
	Stage C	14
	Stage D	2
Etiology		
	alcohol	9 (50.0%)
	HCV-antibodies pos.	5 (27.8%)
	cryptogen	1 (5.5%)
	HBsAg positive	3 (16.7%)
		median (min-max)
Creatinin		0.93 (0.69-2.21)
BUN		14.0 (6.0-69.0)
Bilirubin		1.3 (0.67-4.53)
Protein		73.5 (60.7-92.9)
Albumin		35.2 (24.1-52.7)
Cholinesterase		3.33 (1.00-7.29)
AP		186.5 (109.0-1018.0)
AST		81 (41-453)
ALT		64 (25-192)
γGT		234 (61-818)
CRP		1.26 (0.11-10.78)
AFP		163.4 (2.70-50,000.00)
CA 19-9		89 (1-638)
Erythrocytes		4.0 (3.1-5.2)
Haemoglobin		12.95 (10.4-16.1)
Haematocrit		38.5 (30.6-47.5)
Thrombocytes		135 (52-511)
Leucocytes		7.15 (3.74-10.69)
MCV		92.95 (76.70-105.00)
PT		74 (33-131)

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Table 2, Adverse events/symptoms

Adverse event	*Number (percentage)*
Anaemia	5 (27.8%)
Thromboytopenia	9 (50.0%)
Hypokalemia	0
urinary tract infection	0
Other infections (SBP)	2
Hyperlipidemia	0
Diarrhoea	3 (17%)
Edema	9 (50%)

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