

Combination Therapy of Sirolimus and Sorafenib for Recurrent Hepatocellular Carcinoma after Liver Transplantation

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Abstract

Backgrounds: Sirolimus and sorafenib both have been used in recurrent Hepatocellular Carcinoma (HCC) patients after Liver Transplantation (LT). In the present study, we evaluated the side effects and efficacy of a combination therapy consisting of sirolimus and sorafenib.

Methods: We retrospectively reviewed patients who had recurrent HCC after LT between 2005 and 2012. Toxicity was evaluated by reviewing medical records for each follow-up visit. Efficacy was evaluated according to the modified RECIST guidelines.

Results: A total of 24 patients who received combination therapy were reviewed to evaluate drug toxicity. Side effects included hand-foot syndrome (n=12, 50%), diarrhea (n=7, 29.2%), fatigue (n=2, 8.3%), and alopecia (n=1, 4.2%). Among the 24 patients enrolled in this study, 19 were evaluated for efficacy. A complete response was observed in only 1 case (5.3%), while a partial response was observed in 2 cases (10.5%). Five cases (26.3%) showed disease stabilization. The median overall survival after initiation of the combination therapy was 21.6 months. In comparison, 26 recipients with recurrent HCC received non-combination therapy. The median survival of patients receiving a non-combination therapy was 12.0 months. However, there was no statistically significant difference in patient survival rate between the combination and non-combination therapy groups ($P=0.101$).

Conclusion: Combination therapy of sorafenib and sirolimus for recurrent HCC LT recipients may be useful for disease management. However, controlled prospective study is needed to further evaluate the safety and efficacy of combined sorafenib and sirolimus therapy.

Keywords: Hepatocellular carcinoma; Sirolimus; Sorafenib; Liver transplantation; Tumor recurrence

Introduction

Hepatocellular carcinoma (HCC) is a common solid tumor. At present, the only curative treatment options for HCC are liver resection and liver transplantation (LT). However, recurrent HCC after LT remains one of the major problems in overcoming this disease. Specifically, the rate of HCC recurrence after LT is approximately 10-30% [1]. Surgical resection is the treatment of choice for local recurrence, but this approach is often not possible in many cases due to extra-hepatic tumor dissemination. Furthermore, conventional cytotoxic chemotherapy exhibits low efficacy [2].

Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been shown to have a direct anti-tumorigenic effect and to inhibit cell growth [3]. Likewise, sorafenib, a multiple tyrosine kinase inhibitor, has recently been approved as a first-line treatment for advanced HCC and is recommended by the Barcelona Clinical Liver Cancer (BLCL) staging system [4]. Importantly, sorafenib has been shown to increase survival in advanced cases of HCC [5].

A few studies have assessed the safety and efficacy of concomitant administration of sorafenib and mTOR inhibitors, with results suggesting that a combination therapy approach may have a synergistic effect on HCC. In support of this possibility, combination therapy has been shown to have both anti-proliferative and anti-angiogenic effects [6]. In the present study, we evaluated the safety and efficacy of a combination therapy of sirolimus and sorafenib in patients with HCC recurrence after LT. In addition, we compared the combination therapy with other non-combination treatments according to patient survival.

Patients and Methods

Patients

In this retrospective study we enrolled patients who had been treated with both the mTOR inhibitor sirolimus and the multiple tyrosine kinase inhibitor sorafenib for HCC recurrence after LT. None of the patients were susceptible to locoregional treatments including excision, transarterial chemoembolization (TACE), and radiofrequency ablation (RFA). All patients who were suspected of recurrent HCC were immediately changed from an immunosuppressant to an mTOR inhibitor. Sorafenib treatment was initiated at a dosage of 400 mg/day. A total of 24 patients were enrolled to evaluate safety, while 19 patients were evaluated for efficacy; 5 patients were excluded because of hepatic recurrence only (n=1), locoregional treatment (n=2), and loss during follow-up (n=2). Toxicity was evaluated by reviewing medical records.

In addition, 26 patients treated between January 2005 and December 2007 was reviewed to evaluate the efficacy of non-combination therapy.

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Non-combination therapy included radiotherapy and conventional chemotherapy.

Surveillance after treatments

Patients were followed every 2-3 months to assess patient response to therapy. Follow-up included physical examination, serum AFP, PIVKA-II, liver function tests, and chest X-ray. Helical dynamic triple phase CT was performed every 3 months for the detection of local tumor progression, new intra-hepatic recurrence, and extrahepatic metastasis. MRI and/or positron emission tomography (PET) scan were performed when CT was not definitive. Radiological evaluation of treatment responses was performed according to the modified Response Evaluation Criteria in Solid Tumors (mRECISTs) [7].

Immunologic regimens after transplantation

Tacrolimus, steroids, and mycophenolatemofetil (MMF) were the primary agents used for immunosuppression after liver transplantation. All transplant recipients were given 500 mg of intravenous methylprednisolone during the anhepatic phase until postoperative day two, was tapered to 60 mg per day for a period of five days, and then administered at 8 mg, twice per day, for one month starting on postoperative day eight. Tacrolimus treatment was started on postoperative day three, and the optimal blood level was adjusted to maintain a trough plasma concentration of 10-15 ng/mL during the first month and was reduced to 5-10 ng/mL thereafter. MMF was used in combination with tacrolimus and steroids. Starting on postoperative day one, 750 mg MMF was administered twice a day. Cyclosporin (plasma concentration adjusted to 100-200 ng/mL) was used in the event of Tacrolimus toxicity or Tacrolimus refractory rejection, and was given orally twice a day.

Statistical analysis

Overall survival between groups was determined by Kaplan-Meier methods and differences assessed by the log-rank test. We confirmed the consumption that hazard ratio in patient survival curve between groups was equivalent prior to analysis. The Statistical Package for the Social Sciences (SPSS) version 21 for Windows was used for all tests. P-values less than 0.05 were considered statistically significant.

Results

Clinical characteristics of patients who were treated with combination therapy and non-combination therapy are noted in Table 1. The most common side-effects of the combination therapy were hand-foot reaction (n=12, 50%), diarrhea (n=7, 29.2%) and fatigue (n=2, 8.3%). Eight patients temporarily stopped the therapy due to side effects, but restarted after symptoms subsided.

Sites of HCC recurrence are shown in Table 2. Seven patients exhibited a partial response and stable disease. Only one patient exhibited a complete response of lung metastasis. Tumors progressed in 8 patients (Table 3).

The median overall survival after treatment was 21.6 months (95% confidence interval [CI]: 7.6 -35.6 months). Median disease progression after treatment was 7.6 months (95% CI: 3 -11 months). We also evaluated the efficacy of non-combination therapies, which included conventional systemic chemotherapy and radiotherapy. Conventional chemotherapeutic agents were doxorubicin with cisplatinum or 5-fluorouracil(5-FU) with cisplatinum, and radiation therapy was used for tumor regression. The median survival of non-combination therapy was 12.0 months (95% CI: 1.0 - 18.9 months).

	Combination therapy(n=24)	Non-combination therapy(n=26)
Age [median (range)]	57(25 ~77)	49(29 ~ 74)
Gender [Male: Female n(%)]	22(91.7) : 2(8.3)	19(73.1) : 7(26.9)
Diagnosis [n(%)]		
HCC with HBV	21(87.5)	24(92.3)
HCC with HCV	1 (4.5)	1(3.3)
HCC with NBNC	1 (4.5)	1 (3.3)
HCC with cholangiocarcinoma	1 (4.5)	
Beyond Milan criteria [n(%)]	15(62.5)	18(69.2)
Time of recurrence from LT (months) [median (range)]	9.5 (2.8 ~ 40.2)	10.9 (3.0 ~ 32.4)
Child-Pugh class [n(%)]		
A	15(62.5)	21(80.7)
B	7(29.2)	5(19.3)

* HCC:hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: non hepatitis B or C virus; LT: liver transplantation

Table 1: Clinical characteristics of patients treated with either combination therapy or non-combination therapy.

	N	%
Extra-hepatic recurrence without liver involvement	15	62.5
Hepatic recurrence	1	4.2
Extra-hepatic and hepatic recurrence	8	33.3
Total	24	100.0

Table 2: Site of hepatocellular carcinoma recurrence after liver transplantation in the combination therapy group.

	N	%
Complete response	1	5.3
Partial response	2	10.5
Stable disease	5	26.3
Progression	8	42.1
Not evaluated	3	15.8
Total	19	100

Table 3: Response to combination therapy.

Side effects of the chemotherapy were pancytopenia (n=3, 33%), severe gastrointestinal upset (n=3, 33%) and renal injury (n=1, 11%). There was no statistically significant difference between the median survival of the groups receiving either combination or non-combination therapy (P = 0.101; Figure 1).

Discussion

An effective strategy for treatment of HCC recurrent after LT has not yet been established. In eastern countries, living donor liver transplantations are performing for more HCC cases in BCLC intermediate stage, and an increased rate of recurrence can be expected. While many patients undergoing surgery with a curative intent have a significantly better prognosis than those who are not candidates for radical treatments [8], distant dissemination of tumors is sometimes identified in the early period after transplantation.

In transplant recipients, tumor growth may be promoted by calcineurin inhibitors (CNI) [9,10]. The combination therapy of an mTOR inhibitor and sorafenib has a synergistic effect in preclinical models, and is a potential treatment option for advanced HCC after LT. Other studies have suggested that an immunosuppressive dose of an mTOR inhibitor could be useful for treating recurrent HCC after LT [11]. However, national insurance program in Korea do not cover the use of mTOR inhibitor in recurrent HCC. The side effects of the combination therapy used in this study were not severe, and thus were

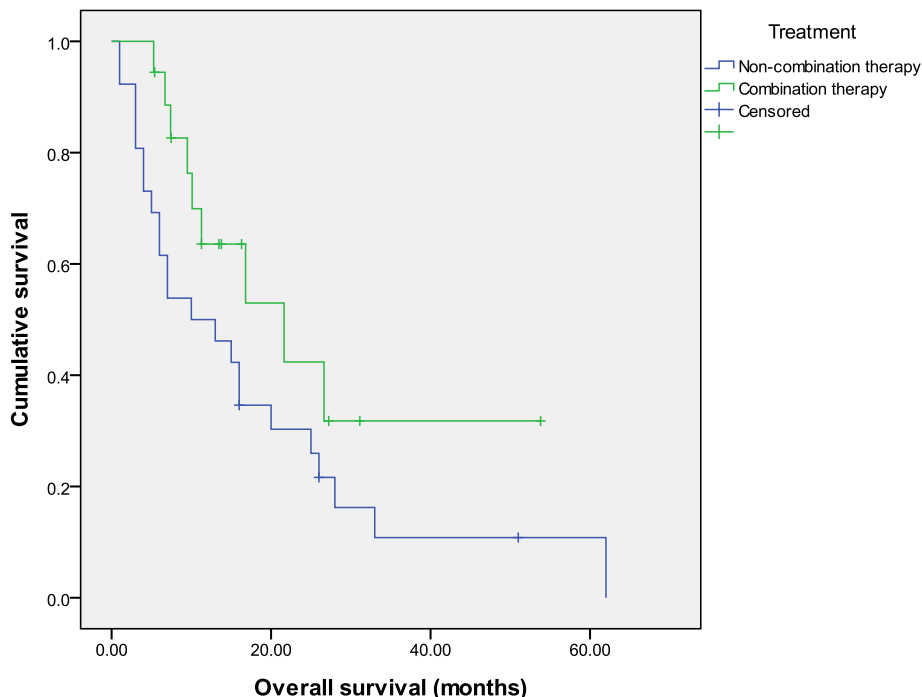


Figure 1: Overall survival after treatment ($P = 0.101$).

considered tolerable. The most common causes of discontinuation of the medication were hand-foot reaction and gastrointestinal upset. However, side effects including bone marrow suppression, hemorrhage and reversible elevation of liver function tests have been observed in other studies [5,12], thus patients must be carefully monitored for signs of toxicity.

The median overall survival in patients with combination therapy was increased compared with conventional non-combination systemic chemotherapy or locoregional treatment, similar to previously described results [13]. However, in this study, there was no statistical significance in survival analysis between treatment groups.

There were some limitations to this study, the first of which was the heterogeneous nature of the non-combination treatment methods. In addition, for the combination therapy group, radiation therapy was administered in patients who had lung and lymph node metastasis, which may have made it difficult to evaluate an exact mechanism of efficacy of the combination therapy. A second limitation of this study was that it was retrospective in nature and involved a small number of cases. Finally, the present study utilized a relatively short follow up period in the combination therapy group due to the use of sorafenib after 2008.

In conclusion, combination therapy of sorafenib and sirolimus for recurrent HCC LT recipients may be useful for disease management. However, controlled prospective study is needed to further evaluate the safety and efficacy of combination therapy using sorafenib and sirolimus for the treatment of recurrent HCC after LT.

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