

Figure 7 mRNA expression of Toll-like receptors and inflammatory cytokines in primary Kupffer cells treated with palmitic acid (PA). Treatment by PA for 24 h induced deposition of fat droplets in primary Kupffer cells (a: control, b: treatment with 10 μM PA, BODIPY (green), 4'6'-diamidino-2-phenylindole dihydrochloride (DAPI) [blue]). The expression of TLR2, TLR4, TLR5, and TLR9 was significantly higher in primary Kupffer cells treated with 10 μM PA for 24 h (C: control) (c). Immunocytochemistry demonstrated that the expression of phospho-interleukin-1 receptor-associated kinase 1 (pIRAK1) was strongly positive in fat deposited primary Kupffer cells treated with 10 μM PA for 24 h (d: BODIPY (green), pIRAK1 (red) and DAPI (blue). Arrow: Kupffer cells deposited in fat droplets. Arrow head: Kupffer cell deposited in absence of fat droplets). Tumor necrosis factor (TNF) expression was significantly higher in primary Kupffer cells treated with 10 μM PA for 24 h (IL-1β (e), TNF (f)) (* $P < 0.05$, ** $P < 0.01$).

We used a mouse model gut-sterilized with antibiotics to confirm whether there is an association between gut microbiota and TLR expression in NAFLD. In our model, oral caloric intake was not significantly different between FA and FC mice, but, body weight, serum ALT levels, and serum free fatty acids levels were significantly suppressed in the FA mice. Furthermore, histopathological findings showed a marked decrease in steatosis in this group. Interestingly, the expression of TLRs and downstream cytokines was suppressed in FA mice compared with that in FC mice. In contrast, in an ethyl alcohol-induced liver injury model, liver TLR expression was found to be independent of gut microbiota despite a decrease in fatty liver and liver injury by antibiotic administration.⁹ Our findings suggest that, directly or

indirectly, gut microbiota contribute to TLR expression in the liver of the NAFLD model. Because antibiotics administration also decreased serum free fatty acids in FA mice, we focused on the association between fatty acid metabolism and gut microbiota. There are three reasons for the suppression of serum free fatty acids in FA mice. The first is a decrease in adipocytes accompanied by suppression of increasing body weight. This may be explained by the fact that obesity-associated microbiota, which increase the capacity to harvest energy from the diet, were eradicated by antibiotics.¹³ We investigated 16S rRNA based analysis of fecal microbiota by the terminal restriction fragment length polymorphism method and confirmed alteration in fecal microbiota of FA mice compared with that of FC

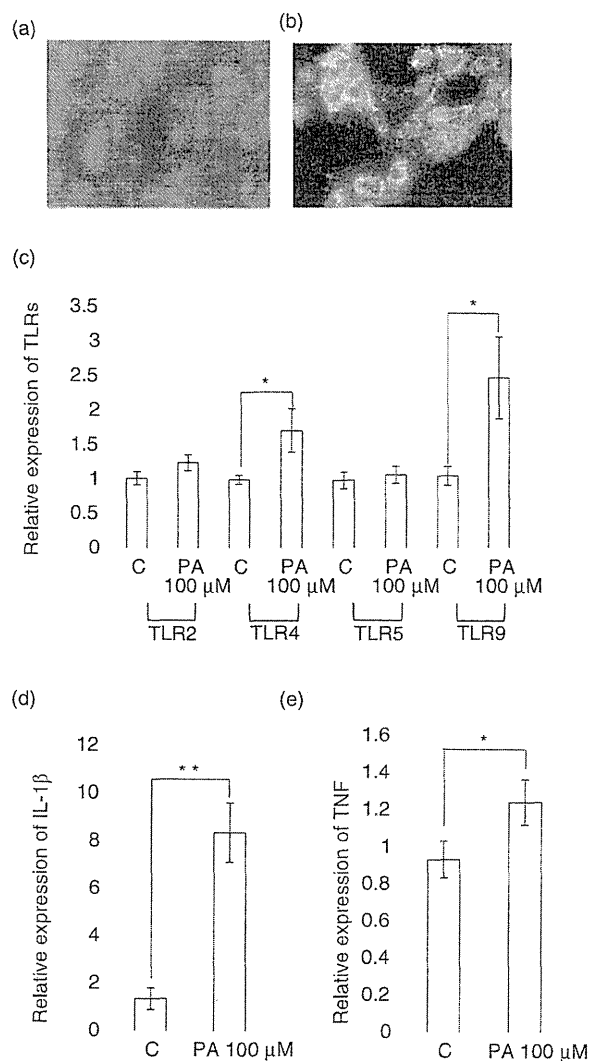


Figure 8 mRNA expression of Toll-like receptors and inflammatory cytokines in primary hepatocytes treated with palmitic acid (PA). Treatment by PA for 24 h induced the deposition of fat droplets in primary hepatocytes (a: control, b: treatment with 100 μM PA, BODIPY (green), 4',6'-diamidino-2-phenylindole dihydrochloride (DAPI) [blue]). The expression of TLR4 and TLR9 mRNA was significantly upregulated in primary hepatocytes treated with 100 μM PA for 24 h (C: control) (c). The expression of tumor necrosis factor (TNF) and interleukin (IL)-1β was significantly higher in primary hepatocytes treated with 100 μM PA for 24 h (IL-1β (d), TNF [e]) (* $P < 0.05$, ** $P < 0.01$).

mice (data not shown). The second reason is a decrease in the release of free fatty acids from adipocytes. In obese individuals, it has been reported that gut microbiota can suppress the expression of fasting-

induced adipose factor (Fiaf), which increases the activity of lipoprotein lipase, leading to the production of triglyceride storage in adipocytes and an increased supply of fatty acids.³² The expression of intestinal Fiaf was significantly upregulated in FA mice compared with FC mice in our experiment (data not shown), indicating that gut-sterilization may contribute to a reduction in the release of serum free fatty acids from adipocytes through increased intestinal Fiaf expression. The third reason is a decrease in *de novo* liver lipogenesis. It is reported that microbiota can increase hepatic lipogenesis through the expression of sterol response element binding protein 1 (SREBP1) and carbohydrate response element binding protein (ChREBP).³³ The expression of both SREBP1 and ChREBP was significantly suppressed in FA mice compared with that in FC mice in our experiment (data not shown), indicating that the suppression of serum free fatty acids, at least in part, contributes to a decrease in hepatic *de novo* lipogenesis through the suppression of both SREBP1 and ChREBP. Our findings suggest both alteration in microflora and a decrease in *de novo* lipogenesis in the liver of the gut-sterilized model, but it is unknown whether the release of free fatty acids from adipocytes decreases.

Next, we hypothesized that fatty acids could alter TLRs expression in the liver. We showed that the expression of TLR2, TLR4, TLR5, TLR9, and TNF were significantly higher in primary Kupffer cells treated with PA than in control cells, while that of TLR4, TLR9, TNF, and IL-1β was upregulated in primary hepatocytes treated with PA. Although our *in vitro* study suggests that PA directly stimulates the induction of TLRs, others report that saturated fatty acids (SFA) including PA stimulate NFκB promoter activity through the activation of the TLR signal pathway. It is also reported that SFA plays a role as TLR4 ligand.^{34,35} Therefore, the induction of downstream cytokines may have contributed to both the upregulation of TLRs and stimulation of TLR4 by PA. These findings suggest that Kupffer cells and hepatocytes are susceptible to bacterial components via upregulation of TLRs by PA in the pro-inflammatory state of NAFLD.

In contrast, although TLRs expression in the small intestine of HFD-fed mice was not altered by antibiotic treatment, it was downregulated in control mice. Therefore, we hypothesized that luminal HFD itself could attenuate TLRs expression in the small intestine. Caco2 cells that are human epithelial cell lines treated with PA or OA showed lower expression of TLR2, TLR5, and TLR9 compared with control cells (data not shown). These data suggest that fatty acids may partly contribute

to the attenuation of TLRs expression in the small intestine.

In conclusion, TLRs expression was downregulated in the NAFLD small intestine, and this may be contributed to an increase in free fatty acids through alteration of gut microbiota. In contrast, the hepatic TLR signal pathway was upregulated and susceptible to microbial components by increased free fatty acids in the pro-inflammatory state of NAFLD. Our findings suggest that discrepancy in TLR signals in the gut-liver axis may be associated with the pathogenesis of progression to NASH through an increase in free fatty acids. Because there is no specific treatment for human NASH, early intervention in the pro-inflammatory state may be important for the prevention of its development from simple steatosis. Because free fatty acids play an important role in the development of the pro-inflammatory state of NAFLD, we consider that both fatty acid metabolism and gut microbiota in the pro-inflammatory state may be useful targets for preventive treatment against NASH development.

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Original Article

Dose-finding trial of tolvaptan in liver cirrhosis patients with hepatic edema: A randomized, double-blind, placebo-controlled trial

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Aim: Liver cirrhosis represents the end stage of any chronic liver disease, and it is associated with hepatic edema such as ascites. Many patients with ascites do not respond to diuretic therapy or require administration of diuretics at high doses that can cause adverse events. This 7-day, multicenter, double-blind trial of tolvaptan was designed to determine the optimal dose of tolvaptan for producing the intended pharmacological effect in hepatic edema.

Methods: Liver cirrhosis patients with inadequate diuretic response despite having received a conventional diuretic therapy were enrolled in the trial. Participants were stratified randomly to four groups receiving tolvaptan at 7.5, 15 or 30 mg/day, or placebo as an add-on to conventional diuretics once daily for 7 days. Changes in bodyweight and abdominal circumference were analyzed. Serum sodium concentrations were measured. Safety assessment was performed.

Results: Tolvaptan at 7.5–30 mg/day reduced bodyweight and abdominal circumference compared with placebo. Serum sodium concentrations remained within the normal range in all tolvaptan groups. Serious adverse events were not observed, and most common adverse event was thirst. Tolvaptan at 7.5 mg/day showed the maximum change in bodyweight and abdominal circumference together with preferable tolerability.

Conclusion: Tolvaptan at 7.5 mg/day was considered the optimal dose in liver cirrhosis patients with hepatic edema who showed inadequate response to conventional diuretics.

Key words: aquaretic action, ascites, diuretics, hepatic edema, liver cirrhosis, tolvaptan

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Author contribution: Isao Sakaida, M.D. had full access to all the data in the trial and took responsibility for the integrity of the data and the accuracy of the data analyses and wrote the first draft of the manuscript. All authors contributed to trial concept and design and data analyses, drafted and reviewed the manuscript revisions, and approved the final draft for submission.

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INTRODUCTION

LIVER CIRRHOSIS REPRESENTS the end stage of many chronic liver disease.¹ Hepatic edema including ascites and lower limb edema is the most frequently observed complication in the disease, leading to deterioration in quality of life.^{2,3} Therefore, improvement of hepatic edema is an important therapeutic strategy. Spironolactone, an aldosterone antagonist, either alone or in combination with the loop diuretic furosemide is prescribed as the first-line therapy for management of liver cirrhosis patients with persistent ascites.⁴ Many patients with ascites do not respond to diuretic therapy or require administration of diuretics at high doses that can cause adverse events including activation of the rennin-angiotensin and sympathetic nervous systems, electrolyte disturbances such as dilutional hyponatremia, and worsening of renal function.⁵⁻⁸ Thus, the development of effective drugs other than conventional diuretics is needed for the management of hepatic edema.

Because arginine vasopressin V₂ receptor antagonists promote electrolyte-free water excretion without disrupting electrolyte balance, they are expected to be clinically useful in the treatment of diseases associated with hyponatremia or fluid retention.^{9,10} Tolvaptan, a novel aquaretic agent, is a non-peptide V₂ receptor antagonist.¹⁰⁻¹⁴ By inhibiting reabsorption at the renal collecting tubules, tolvaptan increases electrolyte-free urine excretion without increasing electrolyte excretion.

In the USA,¹¹ tolvaptan at 15–60 mg/day has been approved for the treatment of hyponatremia, and in the EU,¹² tolvaptan within the same dosage range has been approved for the treatment of syndrome of inappropriate antidiuretic hormone. In Japan, tolvaptan at 15 mg/day has been approved for the treatment of heart failure-related edema.⁵

We initiated a program to obtain the additional indication for the treatment of hepatic edema. Therefore, we conducted the phase 2 study to determine an optimal dose of tolvaptan. In our previous, preliminary trial, tolvaptan at dose of 15 mg/day and higher exerted sufficient pharmacological response for improvement of hepatic edema including ascites in liver cirrhosis patients who showed resistance to furosemide.¹⁶

The aim of this trial was to determine the optimal dose of tolvaptan in hepatic edema showing inadequate response to conventional diuretics. The results of this trial will be used as the basis for a pivotal trial to be conducted to obtain an additional indication for tolvaptan in Japan.

METHODS

Trial setting

THE PRESENT TRIAL was a randomized, double-blind, placebo-controlled, multicenter trial conducted by Otsuka Pharmaceutical (the study sponsor). This trial was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice (GCP) guideline at all times.¹⁷ The trial protocol was reviewed and approved by the institutional review board at each trial site, and written informed consent was obtained from all patients after being informed of the trial purpose and the nature of the procedures involved. All authors had access to the study data and had reviewed and approved the final manuscript. This trial is registered on ClinicalTrials.gov (NCT00479336).

Patients

This trial enrolled liver cirrhosis patients with ascites despite undergoing combination therapy with a loop diuretic and an anti-aldosterone drug at the doses from at least 7 days prior to commencement of trial drug administration, as described below. Prior treatment with diuretics needed to meet either one of the dose criteria being used in Japan. If the daily dose of furosemide and other loop diuretics were at least 40 mg and equivalent to 40 mg furosemide, respectively, then the daily dose of spironolactone was set at 25 mg. If the daily dose of spironolactone was at least 50 mg, then the daily dose of furosemide and other loop diuretics were set at 20 mg or equivalent to 20 mg furosemide, respectively.¹⁸

Patients who met the following criteria were randomized to one of the trial groups and allowed to advance to the treatment period to evaluate efficacy of the drug: patients with ascites during pretreatment observation

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period; patients orally treated with conventional diuretics without change in dose or mode of administration from 7 days before start of trial drug administration until final day of pretreatment observation period; patients with stable bodyweight (± 1.0 kg) for 2 days before start of trial drug administration.

The patients were between 20 and 80 years of age and were required to be hospitalized from the start of a 3-day pretreatment observation period until completion of a 14-day post-treatment observation period. Major exclusion criteria were: (i) patients with hepatic encephalopathy (coma scale, ≥ 11);¹⁹ (ii) patients with poorly controlled hepatocellular carcinoma; (iii) patients requiring new treatment for esophageal or gastric varices; (iv) patients with hemorrhoidal hemorrhage secondary to rectal varices; and (v) patients receiving blood products including albumin preparations.

Treatment protocol

This trial consisted of a 3-day pretreatment observation period (defined as baseline), a 7-day treatment period and a 14-day post-treatment observation period. Trial drugs were administered to patients after breakfast. Day 1 was defined as the period from the first to the second administration. Days 2–7 were similarly defined. For all variables, data obtained immediately before the start of trial drug administration were used as baseline data. The day that each patient completed or discontinued the administration of trial drugs was defined as the final dosing day. The dose and mode of administration of conventional diuretics were to remain fixed from 7 days prior to the start of trial drug administration, and to be administered p.o. in combination with tolvaptan throughout the trial period.

Patients were randomized to four groups receiving tolvaptan at 7.5, 15, 30 mg or placebo once daily for 7 consecutive days (defined as the 7.5-mg group, the 15-mg group, the 30-mg group and the placebo group). The registration center allocated the eligible patients to the treatment groups by stratifying them according to the presence/absence of lower limb edema. Random allocation was performed by a trial drug allocation manager from an independent contact research organization after confirmation that the packages containing tolvaptan tablets and matching placebo tablets were indistinguishable in appearance.

Evaluation

The primary end-point was change in bodyweight from baseline at the final dosing day in patients receiving trial drugs as a surrogate marker for improvement of hepatic

edema.¹⁴ The relationship of change in bodyweight and dose of tolvaptan was evaluated by using a linear regression model. Secondary end-points were change in abdominal circumference and increase in daily urine volume.²⁰

Bodyweight was measured before breakfast following urination each day through the treatment period. Abdominal circumference was also measured before breakfast following urination on days 2–3 and on day 7. Changes in bodyweight and abdominal circumference from baseline to the final dosing day in the tolvaptan groups were compared with those in the placebo group.

Cumulative 24-h urine samples were collected after patients had urinated completely before drug administration (after breakfast) each day from the day before the start of trial drug administration until the end of the post-treatment period. Urinary sodium concentration was measured. Fluid intake was not restricted and measured values were recorded during the trial period. Mean differences between daily fluid intake and daily urine volume were calculated by the treatment groups. Serum sodium concentration was measured before breakfast (baseline), 4–8 h and 22–24 h post-dose on day 1, and before breakfast on days 2–3, on days 7 and 9, and on days 14–17. If patients discontinued, these values were measured at an appropriate time. Change in serum sodium concentration from baseline to the final dosing day was assessed.

Plasma concentration of tolvaptan was measured at baseline on day 1 (22–24 h) and on day 7 (2–4, 8–16 and 22–24 h).

Safety assessment

Safety assessment was performed throughout the trial period. Safety variables included adverse events, adverse events that occurred before the start of trial drug administration, clinical laboratory tests, vital signs and electrocardiograms.

Statistical analysis

For the change from baseline to the final dosing day, ANOVA was performed for pair-wise comparison between each of the tolvaptan groups and the placebo group. The other continuous data were analyzed by ANOVA. The category data were analyzed by Fisher's exact test or Kruskal–Wallis test. None of the analyses were adjusted for multiple comparison. Linear regression analysis was performed by using the change in bodyweight from baseline at the final dosing day as the objective variable and the dose of tolvaptan as the explanatory variable.

Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SAS ver. 9.1.3 software (SAS Institute, Cary, NC, USA).

RESULTS

Patients

THIS TRIAL WAS conducted from June 2007 through July 2008 at 44 institutions. Of 104 patients who received at least one dose of the trial drug, two patients who were in deviation of GCP and one patient who received the trial drug at a dose higher than the specified daily dose at first dosing day were excluded from all analysis sets (Fig. 1).

A total of 101 patients were included in the safety analysis set, comprising 26 patients in the placebo group, 25 in the 7.5-mg group, 25 in the 15-mg group and 25 in the 30-mg group. One patient in the placebo group was not included in the efficacy analysis set because this patient underwent abdominal paracentesis on day 3. One missing data existed each in abdominal circumference analysis and urine volume analysis. Demographic and other baseline characteristics are shown in Table 1. No notable differences in background factors were observed among the four groups.

Efficacy of study drug

Change in bodyweight from baseline was -0.36 kg (standard deviation [SD], 2.06) in the placebo group, -2.31 kg (SD, 2.35) in the 7.5 mg group, -1.88 kg (SD, 2.45) in the 15 mg group and -1.67 kg (SD, 1.46) in the 30 mg group (Fig. 2). Change in bodyweight in all tolvaptan groups showed significant decreases compared with the placebo group ($P = 0.014$ for the 7.5-mg group, $P = 0.011$ for the 15-mg group and $P = 0.029$ for the 30-mg group). The regression coefficient of the dose was not statistically significant ($P = 0.3157$).

Change in abdominal circumference from baseline was -1.0 cm (SD, 2.8) in the placebo group, -3.0 cm (SD, 3.2) in the 7.5-mg group, -2.4 cm (SD, 2.5) in the 15-mg group and -2.6 cm (SD, 2.8) in the 30-mg group. Tolvaptan at 7.5 mg was significantly superior ($P = 0.030$) to the placebo in Figure 3.

Change in daily urine volume is shown in Figure 4. Increases in daily urine volume in all tolvaptan groups were observed in a dose-dependent manner. The differences in the change in urine volume between each tolvaptan group and the placebo group were statistically significant. All tolvaptan groups showed maximum increases in urine volume on day 1.

Serum sodium concentration in all tolvaptan groups increased, and further remained within the normal

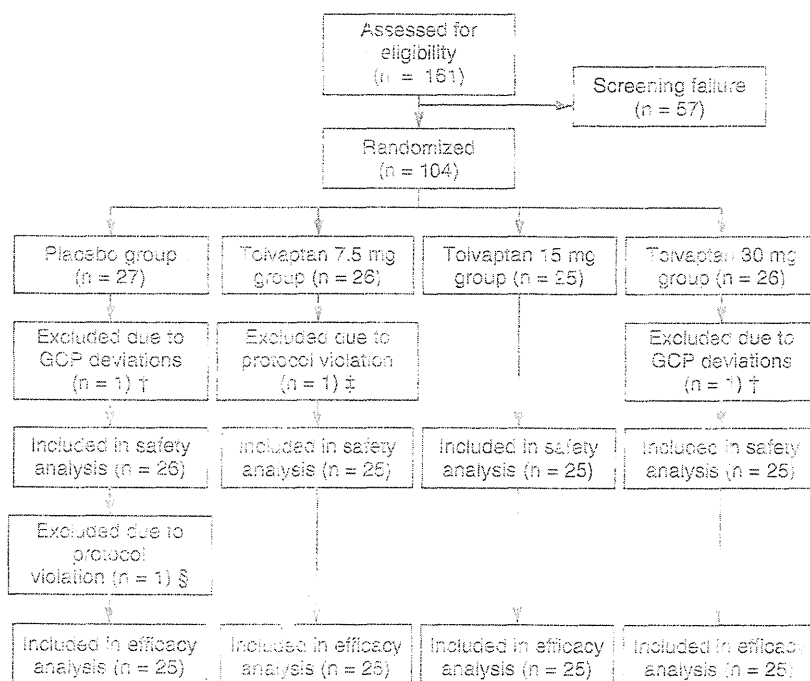


Figure 1 Patient flow chart. †Registration before the approval of the institutional review board. ‡Violation regarding specified daily dose. §Patient underwent abdominal paracentesis. GCP, Good Clinical Practice.

Table 1 Demographic and clinical characteristics at baseline

| Characteristics | Placebo group (n = 26) | 7.5-mg group (n = 25) | 15-mg group (n = 25) | 30-mg group (n = 25) | P-value |
|--|---------------------------|--------------------------|-------------------------|-------------------------|---------|
| Age (years) | 64 (10) | 65 (9) | 65 (10) | 63 (10) | 0.89† |
| Sex (male) | 17 (65.4%) | 18 (72.0%) | 21 (84.0%) | 15 (60.0%) | 0.27‡ |
| Bodyweight (kg) | 57.8 (11.6) | 61.9 (10.8) | 59.1 (11.4) | 60.0 (12.1) | 0.62† |
| Abdominal circumference (cm) | 86.6 (9.0) | 89.8 (9.4) | 86.6 (9.5) | 88.6 (11.4) | 0.58† |
| Cause of liver cirrhosis | | | | | |
| Hepatitis B | 4 (15.4%) | 4 (16.0%) | 4 (16.0%) | 0 (0.0%) | |
| Hepatitis C | 13 (50.0%) | 13 (52.0%) | 6 (24.0%) | 17 (68.0%) | |
| Alcoholic cirrhosis | 6 (23.1%) | 7 (28.0%) | 7 (28.0%) | 4 (16.0%) | |
| Other | 3 (11.5%) | 4 (16.0%) | 0 (0.0%) | 5 (20.0%) | |
| Child-Pugh classification | | | | | 0.98§ |
| A | 0 (0.0%) | 1 (4.0%) | 0 (0.0%) | 2 (8.0%) | |
| B | 16 (61.5%) | 13 (52.0%) | 15 (60.0%) | 13 (52.0%) | |
| C | 10 (38.5%) | 11 (44.0%) | 0 (0.0%) | 10 (40.0%) | |
| Complication of liver cancer | 10 (38.5%) | 11 (44.0%) | 9 (36.0%) | 10 (40.0%) | 0.97‡ |
| Serum albumin concentration (g/dL) | 2.8 (0.5) | 2.7 (0.5) | 2.8 (0.5) | 2.9 (0.6) | 0.70† |
| Serum creatinine concentration (mg/dL) | 0.9 (0.3) | 0.9 (0.3) | 1.0 (0.4) | 0.8 (0.2) | 0.21† |

Data are expressed as mean (standard deviation) or number of patients (%).

†ANOVA.

‡Fischer's exact test.

§Kruskal-Wallis test

range. The placebo group showed no change in serum sodium concentration (Fig. 5). Changes in serum sodium concentration from baseline to the final dosing day were -0.7 mEq/L (SD, 2.0) in the placebo group, 1.2 mEq/L (SD, 3.0) in the 7.5-mg group, 2.8 mEq/L (SD, 3.1) in the 15-mg group and 3.2 mEq/L (SD, 3.9) in the 30-mg group. All tolvaptan groups showed significant differences compared with the placebo group (7.5-mg group, $P=0.029$; 15-mg group, $P<0.001$; 30-mg group, $P<0.001$). Mean differences between daily fluid intake and daily urine volume were 601 mL in the placebo group, 1190 mL in the 7.5-mg group, 1245 mL in the 15-mg group and 1494 mL in the 30-mg group.

Time-courses of plasma tolvaptan concentrations are shown in Figure 6. Plasma tolvaptan concentration at 2–4 h post-dose on day 7 was 55 ng/mL (SD, 44) in the 7.5-mg group, 164 ng/mL (SD, 137) in the 15-mg group and 300 ng/mL (SD, 226) in the 30-mg group.

Safety assessment

Adverse events that occurred at an incidence of at least 5% are shown in Table 2. The most commonly reported adverse event was thirst in all tolvaptan groups, showing a dose-dependent increase. Thirst was also observed in one patient in the placebo group. Other adverse events

that occurred frequently in the tolvaptan groups were pollakiuria, insomnia, and increased blood uric acid, blood urea and blood alkaline phosphatase.

Serious adverse events were observed as follows: anemia, abdominal distension, chronic hepatitis, hepatic failure, hepatitis B, dyspnea and hepatorenal syndrome in the placebo group; renal impairment and hemorrhagic shock in the 15-mg group; and gastrointestinal hemorrhage, hepatic failure and hepatic encephalopathy in the 30-mg group.

Changes in creatinine from baseline at the final dosing day were -0.001 mg/dL in the placebo group, 0.041 mg/dL in the 7.5-mg group, 0.057 mg/dL in the 15-mg group and 0.072 mg/dL in the 30-mg group.

DISCUSSION

IN THE PRESENT trial, tolvaptan at daily doses of 7.5, 15 and 30 mg demonstrated notable pharmacological effect including improvement of hepatic edema in liver cirrhosis patients in comparison with placebo. Tolvaptan at 7.5 mg/day showed the maximum change in bodyweight and abdominal circumference. Preferable tolerability was shown at 7.5 mg of tolvaptan. Therefore, tolvaptan at 7.5 mg/day was considered the optimal dose in the treatment of hepatic edema.

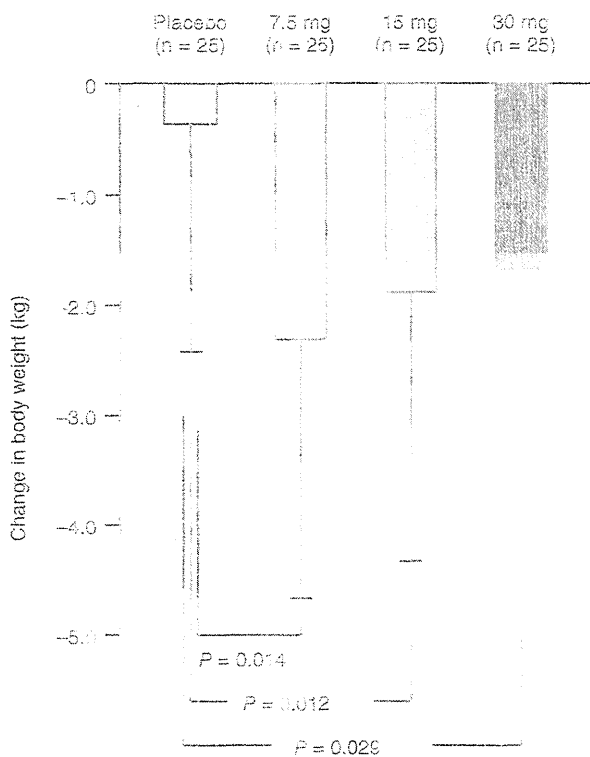


Figure 2 Changes in body-weight from baseline at the final dosing day. Data are expressed as mean \pm standard deviation. Contrast tests between each tolvaptan group and the placebo group were performed by using multiplicity-unadjusted ANOVA.

The present trial was conducted to determine the optimal dose of tolvaptan based on the results of our previous trial.¹⁶ In that previous trial, the targeted pharmacological action as reduction in bodyweight was confirmed at tolvaptan doses of 15 mg and higher. In the present trial, in addition to that same tolvaptan dose of 15 mg, a half dose (7.5 mg) and a double dose (30 mg) were also evaluated. No linear dose response to change in bodyweight was observed, while urine volume and fluid intake showed a dose-dependent manner. However, the largest reduction in bodyweight was observed in the 7.5-mg group. Investigation at doses of tolvaptan less than 7.5 mg/day may be required. Various factors can be considered, water restriction was not included as a rule and regulation in this trial. Thirst was observed in a dose-dependent manner, therefore, it may be one of the major factors.

Hyponatremia is one of the problems in loop diuretic therapy. Serum sodium concentration was signifi-

cantly increased in the tolvaptan groups, but not in the placebo group, indicating that tolvaptan produced improvement of electrolyte imbalance. This is caused by tolvaptan's aquaretic action.¹⁴⁻¹⁶ This result demonstrated that tolvaptan in combination with conventional diuretics contributes to treating cirrhotic patients with hepatic edema.¹⁴

Plasma tolvaptan concentration at 2–4 h post-dose on day 7 was 55 ng/mL (SD, 44) in the 7.5-mg group, 164 ng/mL (SD, 137) in the 15-mg group and 300 ng/mL (SD, 226) in the 30-mg group. Kim *et al.* reported that following administration of tolvaptan at 30 mg in healthy subjects for 7 days, plasma tolvaptan concentration attained a maximum of 198 ng/mL (SD, 32) within 2–4 h post-dose.²¹ Plasma tolvaptan concentration in liver cirrhosis patients with hepatic edema are considered to be higher than in healthy subjects. Tolvaptan is metabolized exclusively in the liver, primarily by cytochrome P450 3A4.²⁴ Therefore, plasma

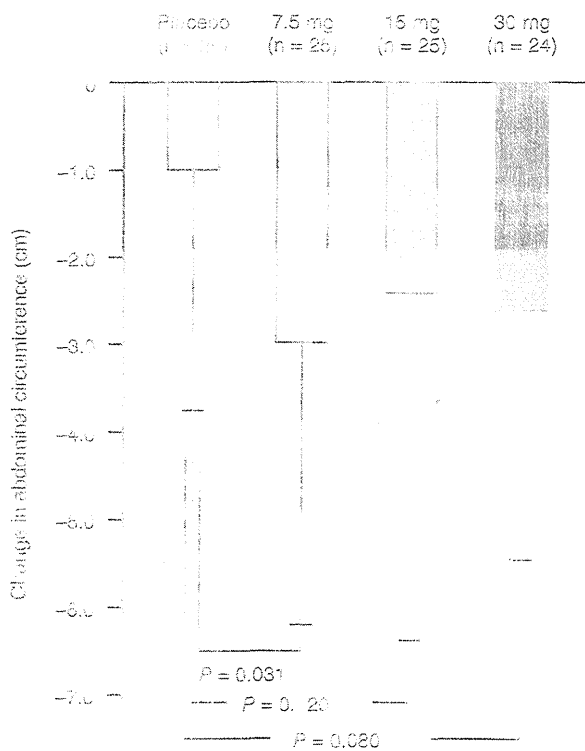


Figure 3 Changes in abdominal circumference from baseline at the final dosing day. Data are expressed as mean \pm standard deviation. Contrast tests between each tolvaptan group and the placebo group were performed by using multiplicity-unadjusted ANOVA.

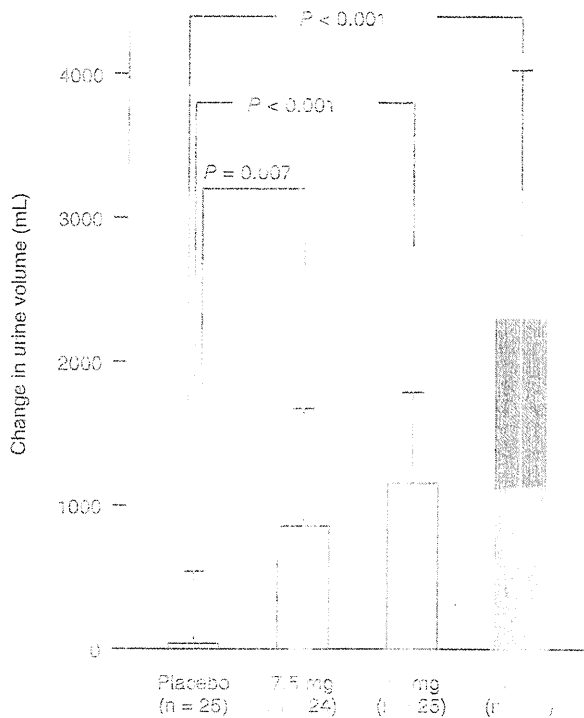


Figure 4 Changes in daily urine volume from baseline to the final dosing day. Data are expressed as mean \pm standard deviation. Contrast tests between each tolvaptan group and the placebo group were performed by using multiple-comparison unadjusted *t*-test.

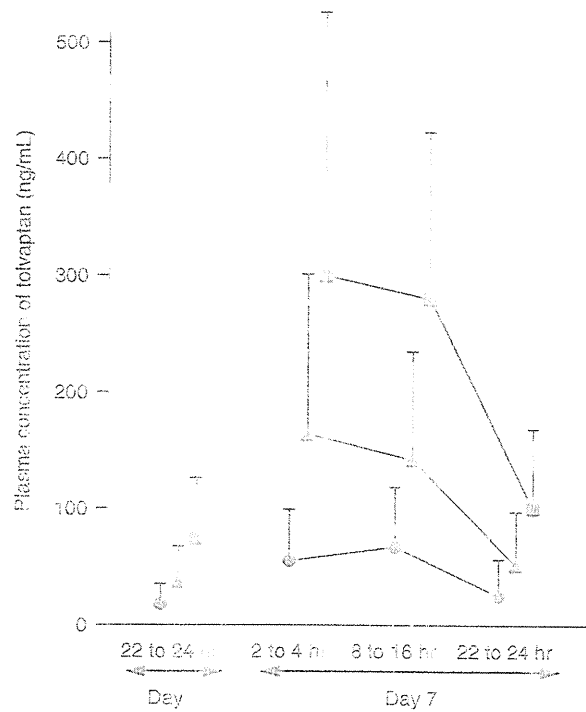


Figure 6 Time courses of plasma tolvaptan concentration. Data are expressed as mean \pm standard deviation. ○, 7.5 mg; ◐, 15 mg; ◑, 30 mg.

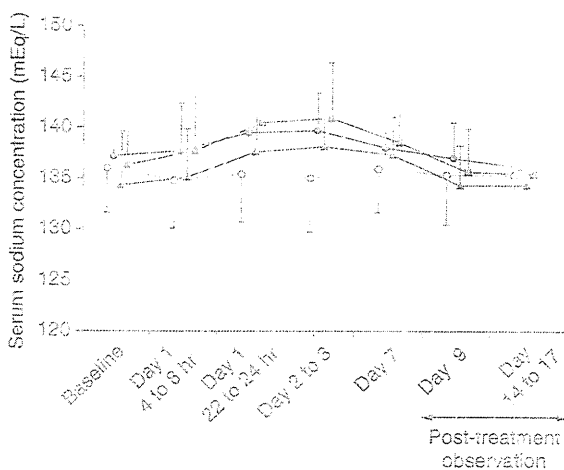


Figure 5 Time courses of serum sodium concentration. Data are expressed as mean \pm standard deviation. ○, placebo; ◐, 7.5 mg; ◑, 15 mg; ◒, 30 mg.

concentration of tolvaptan in patients with hepatic dysfunction or cirrhosis may be higher than that in patients with normal hepatic function.

Although the satisfactory results were obtained, the present trial was limited in that it did not include an evaluation of tolvaptan's potential for improving ascites volume and symptoms related to hepatic edema. Therefore, the next trial should be designed to evaluate tolvaptan's effect on these outcome variables in liver cirrhosis patients.

In conclusion, tolvaptan at 7.5 mg/day showed the maximum change in body weight and abdominal circumference together with preferable tolerability. Therefore, tolvaptan at 7.5 mg/day was considered the optimal dose in the treatment of hepatic edema.

ACKNOWLEDGMENT

○ TSUKA PHARMACEUTICAL CO. FUNDED this trial and provided tolvaptan.

Table 2. Incidence of adverse events

| Adverse events | Placebo (n = 26) | Tolvaptan | | | Total (n = 75) |
|--------------------------------------|---------------------|-----------------|----------------|----------------|----------------|
| | | 7.5 mg (n = 25) | 15 mg (n = 25) | 30 mg (n = 25) | |
| Total | 22 (84.6) | 22 (88.0) | 22 (88.0) | 25 (100.0) | 69 (92.0) |
| Observed in $\leq 5\%$ of patients | | | | | |
| Thirst | 1 (3.8) | 6 (24.0) | 14 (56.0) | 5 (20.0) | 35 (46.7) |
| Pontalgia | 0 (0.0) | 3 (12.0) | 5 (20.0) | 12 (48.0) | 25 (33.3) |
| Insomnia | 1 (3.8) | 1 (4.0) | 6 (24.0) | 6 (24.0) | 3 (17.3) |
| Blood uric acid increased | 1 (3.8) | 3 (12.0) | 4 (16.0) | 5 (20.0) | 12 (16.0) |
| Blood alkaline phosphatase increased | 1 (3.8) | 5 (20.0) | 3 (12.0) | 2 (8.0) | 11 (14.7) |
| Blood urea increased | 4 (15.4) | 4 (16.0) | 4 (16.0) | 3 (12.0) | 11 (14.7) |
| Constipation | 2 (7.7) | 1 (4.0) | 5 (20.0) | 1 (4.0) | 7 (9.3) |
| Diarrhea | 2 (7.7) | 5 (20.0) | 2 (8.0) | 1 (4.0) | 7 (9.3) |
| Blood creatinine increased | 3 (11.5) | 2 (8.0) | 3 (12.0) | 2 (8.0) | 7 (9.3) |
| Nausea | 1 (3.8) | 1 (4.0) | 3 (12.0) | 2 (8.0) | 6 (8.0) |
| Pyrexia | 3 (11.5) | 1 (4.0) | 3 (12.0) | 1 (4.0) | 6 (8.0) |
| Blood hemoglobin increased | 5 (19.2) | 1 (4.0) | 1 (4.0) | 3 (12.0) | 5 (6.7) |
| Blood osmolality increased | 1 (3.8) | 0 (0.0) | 0 (0.0) | 4 (16.0) | 4 (5.3) |
| Decrease blood pressure | 0 (0.0) | 2 (8.0) | 1 (4.0) | 0 (0.0) | 4 (5.3) |

Data are expressed as number of patients (%).

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Intraluminal duodenal diverticulum with refractory pancreatitis successfully treated by endoscopic diverticulectomy

The current report presents a rare case of intraluminal duodenal diverticulum (IDD), which is a congenital anomaly whereby the formation of a pocket-like diverticulum causes intestinal obstruction and/or refractory pancreatitis.^{1–3} The present case was cured by endoscopic resection with a two-channel procedure.

A 33-year-old woman was admitted to Asahikawa Red Cross Hospital due to frequent epigastralgia. Blood examination revealed high levels of serum amylase (2278 IU/L) and lipase (7227 U/L). Computed tomography showed swelling of the pancreas and an intussusception-like change of the duodenum. She was diagnosed to have acute pancreatitis. After improving the pancreatitis with gabexate mesilate, gastroduodenoscopy detected a pocket-like lesion beside the true lumen in the duodenum. The major Vater's papilla was observed at the septum separating the pocket-like lesion. The pocket-like lesion was easily observed by pulling the bottom of the lesion (Fig. 1A,B). Barium duodenography revealed a 4-cm stagnation framed by a clear and smooth translucent line (Fig. S1). The patient was diagnosed with IDD.

Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography revealed normal bile and pancreatic duct structures without ectopic ducts in the pocket-like lesion. The patient provided written informed consent and the lesion was endoscopically reversed and removed using a two-channel endoscope with no complications (Fig. 2A,B). This procedure allows one to maintain the reverse position of the pocket-like lesion and to clearly observe the cutting site during the resection (Video S1). Histological findings showed a submucosal layer between two mucosal layers, showing a mirror image (Fig. S2). There have been no abdominal symptoms 3 months after treatment, and at the following endoscopy the lesion had disappeared. While endoscopic treatment has been used for removing IDD in several cases,^{4,5} this is the first report to show the efficacy of the two-channel procedure for removing IDD (Table S1).

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

T.I. and M.F. provided major input into the conceptual development of the present report, carried out the endoscopic examinations and treatment and wrote the manuscript. Y.K. prepared/reviewed the manuscript. C.H. found the lesion and took care of the patient.

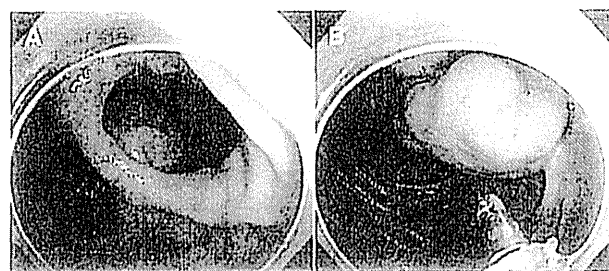


Figure 1 Endoscopic findings of intraluminal duodenal diverticulum (IDD). Gastroduodenal endoscopy revealed a pocket-like lesion beside the true lumen in the duodenum. (A) The major Vater's papilla was observed at the septum separating the pocket-like lesion from the true lumen. (B) The pocket-like lesion was easily observed by pulling the bottom of the lesion, suggesting the lesion contained a mucosal and a submucosal layer, but not a muscle layer or serosa.

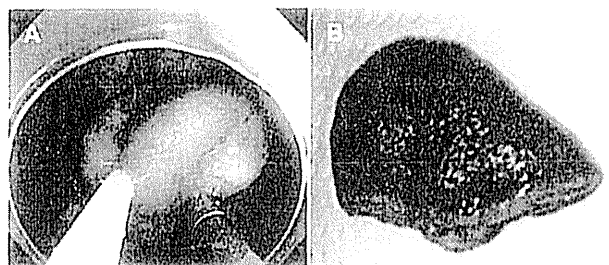


Figure 2 Endoscopic diverticulectomy. (A) The lesion was endoscopically reversed and removed by endoscopic diverticulectomy using a two-channel endoscope. (B) A pocket-like lesion with a smooth surface was removed without any complications.

Authors declare no conflict of interests for this article.

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肝疾患に対する外科治療 肝細胞癌治療の最近の話題

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肝疾患に対する外科治療 肝細胞癌治療の最近の話題

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要 約

肝細胞癌に対して、1980年代より手術治療の進歩とともに、ラジオ波凝固療法、経皮的エタノール注入療法、肝動脈化学塞栓療法（TACE）を組み合わせた集学的治療法が発展し、予後の改善に繋がってきた。近年では従来の治療に加えて、腹腔鏡やロボット（da Vinci）による肝切除術、肝移植、分子標的薬、陽子線療法などの新しい治療法が加わり、更に幅広い集学的治療が可能となってきている。しかしながら、個々の治療に関しては未だ試験段階のものも多い。我々は、新たな知見の集積による治療法・治療戦略の開発はもちろん、定期的なフォローと各科横断的な診療体制の構築が、肝細胞癌の予後向上につながるものと考えている。

Key Words：肝細胞癌，肝切除術，集学的治療

はじめに

肝細胞癌に対して、1980年代より手術治療の進歩とともに、ラジオ波凝固療法、経皮的エタノール注入療法、TACE を組み合わせた集学的治療法が発展し、予後の改善に繋がってきた。近年ではこれらの治療法に加え、腹腔鏡やロボット（da Vinci）による肝切除術、肝移植、分子標的薬、陽子線療法などの新しい治療法が加わり、更に幅広い集学的治療が可能となってきている。

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本稿では肝細胞癌における最近の治療法について概説する。

腹腔鏡下肝切除術

2010年より我が国で腹腔鏡下肝外側区域切除術、腹腔鏡下肝部分切除術が保険収載となり、肝細胞癌に対しても腹腔鏡下肝切除術を導入する施設が増加している。外側区域以外の腹腔鏡下肝切除についても、先進的治療として、種々のアプローチでの導入が報告されている。

非肝硬変患者における腹腔鏡下肝切除（major）の検討では、患者予後と医療コストについては、開腹手術と同様の成績であったが¹⁾、腫瘍の局在によっては、腹腔鏡下肝切除術の方が安全性が高いことが判明した。Slakey, D. Pらは、単施設での腹腔鏡下肝切除45例と開腹肝切除17例の比較において、腹腔鏡下肝切除の方

が合併症 (15.5% vs 52.9%, $p = .007$), 術中出血 (95.0±89ml vs 988.0±1450ml, $p = .0001$) が少なく, ICU 在室日数5日以上 (腹腔鏡3例 vs 開腹5例, $p = .05$), 在院日数10日以上 (腹腔鏡3例 vs 開腹6例, $p = .01$) についても腹腔鏡手術群の方が良好と報告している。特に, 後上区域切除の患者で, 開腹に比して, 腹腔鏡下の方が合併症率が低いのが特徴的であった²⁾。腹腔鏡下肝切除と開腹肝切除を比較した meta-analysis では, 腹腔鏡下肝切除は, 手術時間, 胆汁漏, 術後出血, 肺合併症, 腹腔内膿瘍, 死亡率, 断端陽性率, 再発率には差がなかったものの, 術中出血が129ml 少なく (95% C.I.: 224-36ml, $p = .008$), 輸血の頻度も少なく (オッズ比0.49, 95% C.I.: 0.26-0.91, $p = 0.02$), 在院日数が3.19日短く (95% C.I.=4.09-2.28, $p < 0.00001$), 術後腹水の発生頻度も少なかった (オッズ比0.32, 95% C.I.: 0.16-0.61, $p = 0.006$) と結論づけている³⁾。一方, 腹腔鏡を用いた肝切除術(葉切除)の長期予後に関して述べた論文は少なく, 肝細胞癌に対する腹腔鏡下肝葉切除術後の5年生存率は50-64.9%と報告されており⁴⁾⁵⁾, 開腹肝切除術に比して遜色ない結果と考えられる。

以上より, 背景肝, 合併症などの患者因子と, 解剖学的局在や大きさ, 脈管侵襲などの腫瘍因子を揃えて患者群を比較した場合, 腹腔鏡下肝切除術の周術期合併症の発生率は開腹手術と比して遜色なく, 腹腔鏡下手術では, さらに創が小さいことによる整容性向上や術後疼痛軽減などの利点が得られると思われる。腹腔鏡下肝葉切除術の長期予後に関しては, 今後さらなる症例の蓄積が待たれる。

ロボット (da Vinci) 肝切除術

近年, ロボット手術の導入が積極的に行われるようになり, 肝切除においても施行例が報告されている。単一の術者による30例のロボット肝切除の報告では, 右葉切除6例, 左葉切除14例, その他10例を行い, 平均手術時間は右葉切除724分, 左葉切除518分, 平均出血量は右葉切除629ml, 左葉切除328mlであった。開腹手術移行率は全体で6.7%, 葉切除で10.0%であった。合併症は43% (13例) に認められたが, 肝切除に直接起因する合併症は, 胆汁漏を2例に認めたのみであった。11ヶ月 (中央値) の追跡期間で肝癌の再発は認めていない。この結果を他の腹腔鏡下肝切除の論文⁷⁾と比較・参照することにより, ロボット手術を施行可能

で安全な手技であると結論づけている。手術時間の長さが問題であるが, 今後, 経験の蓄積に伴って短縮されることが期待される。

また, meta-analysis による217例のロボット肝切除術のまとめによると, ロボット肝切除で最も行われている手技は楔状切除と区域切除であった。開腹手術への移行率は4.6%, 移行の理由は, 腫瘍マージンが不明瞭であったとするものが最も多かった。ロボット肝切除手術は腹腔鏡手技に長けた外科医にとっては, 安全に施行可能であり, 周術期合併症などを含めた短期成績は, 従来の腹腔鏡下肝切除術と遜色なかった⁸⁾。

ロボット手術は費用対効果や長期成績がまだ不明であり, 低侵襲性に関する利点と比較検討した今後の研究が待たれる。

陽子線療法

これまでHCCに対する放射線療法は, 正常肝への影響が大きいため, その役割は限定的であった。3次元原体照射や定位照射の進歩によって, 腫瘍への放射線照射を集中できることから, 照射線量の増加が可能となったが, 依然として正常肝への影響は無視できない。陽子線は体内の照射経路においてほとんど放射線を放出しない生理的特質を持ち, 目的とする腫瘍領域へより多量の放射線を照射することが可能である⁹⁾。

本邦での肝細胞癌手術非施行患者への陽子線治療の治療成績は, 162患者の5年生存率が23.5%, 162患者192腫瘍の5年局所制御率が86.9%であった。全死亡例145例の53.1% (77例) は癌死ではなく背景の肝硬変に起因する死亡であり, 局所療法としては十分な成績をあげたものと考えられる¹⁰⁾。また, 10cm以上の肝細胞癌患者22例に対して陽子線療法を行った報告では, 追跡期間13.4ヶ月 (中央値) で, 2年腫瘍制御率は87%, 2年全生存率と無増悪生存率は, それぞれ36%, 24%であった。Grade 3以上の合併症は認めなかった。このことから著者は, 陽子線療法は効果的で安全な治療法であると結論づけている¹¹⁾。

問題として, 我が国で陽子線治療を受けられる施設は数施設に限られていること, 保険適用外となるため治療費が高額 (約300万円) となることがあげられる。

ラジオ波焼灼術 (RFA)

RFAは肝細胞癌に対する局所治療として, 内科的,

外科的に広く行われている。我が国の肝癌診療ガイドラインでは、穿刺局所療法への適応は、Child-Pugh分類 AまたはBの肝機能、腫瘍径3 cm以下かつ腫瘍数3個以下のHCCとされる¹²⁾。さらに、経皮的エタノール注入療法 (PEIT) に比してRFAが局所制御能にすぐれ、生存率を向上した¹²⁾¹³⁾。RFAは一般的に、局所の腫瘍制御、再発抑制、症状緩和、肝切除不可能な患者の予後改善に用いられる。現在、RFAは、限局しているが切除不能なHCC、肝転移に対する原発または補助治療として評されている¹⁴⁾。Cucchettiらのレビューでは、2 cm以下のHCCで解剖学的に穿刺可能なものに対してRFAを行うことが、完全壊死と safety marginの点から推奨されている。2 cm以上または3 cm以上で、焼灼が安全で効果的でない腫瘍に関しては、外科的切除が好ましいようである¹⁵⁾。

Duanらの2編のRCTと10編のnon-RCTを含む論文のMeta-analysisによると、Milan基準 (HCCが単発5 cm以下、多発3個以下でおのおの3 cm以下、遠隔転移、リンパ節転移、Vp2以上の肉眼的脈管浸潤なし) 内のHCCに対する肝切除とRFAの比較では、1年全生存率では有意差はなかったが、1年無増悪生存率、3年、5年の全生存率、無増悪生存率に関しては、肝切除の方がRFAよりも有意に良好であった。合併症率、在院期間についてはRFAの方が有意に良好な結果であった。以上の成績から、肝細胞癌の治療として肝切除が第一選択と考えられた¹⁶⁾。現在我が国において、初発肝癌患者に対するRFAと肝切除のRCTが施行中である (SURF trial)¹⁷⁾。肝細胞癌治療の新たな一歩となるエビデンスが得られることが期待されており、症例の集積が進められている。

全身化学療法/分子標的薬/TACE

進行・切除不能肝細胞癌に対する全身療法としては、2007年のASCOで発表されたSorafenib¹⁸⁾が2009年より我が国でも使用可能となり、広く臨床で使用されている。しかし、Sorafenib以降の治療ラインについては、様々な報告がなされているものの、未だ標準的な治療法はない¹⁹⁾。

肝細胞癌の発癌に関する分子経路としては、Sorafenibの標的であるVEGFR、PDGFR、FGFなどに代表される血管新生関連経路の他、EGFRなどの成長因子、HGF/c-Met、PI3K/Akt/mTORなどの多様な経路が見つかり、それぞれに対する阻害剤が開発され、臨

床試験が行われている²⁰⁾²¹⁾。具体的には、表1に示すような分子標的薬に対して、Phase IからIIIの試験が行われているが²¹⁾、これら以外にエピジェネティックなDNAの修飾に関連した発癌を阻害する薬剤 (Belinostat) も開発されている。切除不能肝細胞癌に対してBelinostatを投与したPhase II試験では、無増悪生存期間と全生存期間はそれぞれ2.64か月と6.60か月、Stable disease rateは45.2%であり²²⁾、許容範囲の毒性で腫瘍の進行を阻止できる薬剤として期待されている。

HCCの発癌経路は非常に多様であり、主となる経路の存在は確認されていない。肝細胞癌の全遺伝子解析において、同一患者の多中心性発生と思われる腫瘍のペアからでも、共通の体細胞変異は同定されなかった²³⁾。Sorafenib以外の新規薬剤に関して、単剤での有効性が明らかであるものは未だ存在せず、個々の腫瘍において活性化している経路に応じた分子標的薬の複合治療が必要となる可能性がある。TACEにより腫瘍内が低酸素環境に置かれることから、VEGFなどの血管新生関連因子が増加することが示されており²⁴⁾、TACEと血管新生阻害剤の組み合わせによる治療の可能性が検討されている²¹⁾。また、Doxorubicin溶解ビーズを用いたTACEとSorafenibの複合治療もPhase II trialが行われており、その効果が期待されている²⁵⁾。

また、近年様々な固形腫瘍において癌幹細胞 (CSCs) の存在が報告されている。最近の研究では上皮-間葉移行 (EMT) とCSCsが密接に関連していることが考えられている²⁶⁾。HCCにおいても、CD133、CD90などの分子がCSC markerとして報告されており、新たなbiomarkerとしての臨床応用が期待される。

肝移植

肝硬変を背景とした肝細胞癌に対する最も根治的な治療は、肝移植である。我が国では、海外に比して脳死肝移植が圧倒的に少なく、慢性的なドナー不足の問題がある。今後、生体肝を含むドナープールの効率的な利用と、移植後の再発抑制と免疫抑制を両立させるレジメンの開発が課題とされる²⁷⁾。

肝細胞癌に対する肝移植適応に関しては、長年Milan基準が世界標準であった。しかし、Milan基準外の進行した腫瘍を持つ患者について、肝移植後、4分の3近くが癌を再発していないことから、これらの患者をいかにして肝移植適応患者として拾い上げるか

表1 肝細胞癌に対する新規標的薬剤の早期治療成績 (文献(20)より引用)

| Agent | Phase | N | Efficacy |
|--|--|----------|---|
| Tivantinib ⁴³ | Randomized Phase II Tivantinib vs placebo ITT population | 71 vs 36 | Median TTP: 6.9 weeks vs 6.0 weeks Median OS: 6.6 months vs 6.2 weeks |
| | e-Met high | 22 vs 15 | Median TTP: 11.7 weeks vs 6.1 weeks Median OS: 7.2 months vs 3.8 weeks |
| Sunitinib | Phase II ⁴⁰ | 34 | Median PFS: 3.9 months Median OS: 9.8 months |
| | Phase III ⁴¹ Sunitinib vs sorafenib | 1073 | Median OS: 7.9 vs 10.2 months; |
| Brivanib | Phase II ⁴² | 55 | Median PFS: 2.7 months Median OS: 10 months |
| | Phase III (BRISK-PS) ⁴³ Brivanib vs placebo | 395 | Median OS: 9.4 months vs 8.3 months TTP: 4.2 months vs 2.7 months RR: 12% vs 2% |
| Linifanib ⁴⁴ | Phase II | 44 | TTP: 5.4 months Median OS: 10.4 months |
| Erlotinib | Phase II ⁴⁵ | 38 | Median OS: 13.0 months |
| | Phase II ⁴⁶ | 40 | Median OS: 10.8 months |
| | Phase III (SEARCH) ⁴⁷ Sorafenib/erlotinib vs sorafenib/placebo | 362 | Median OS: 9.5 months vs 8.5 months TTP: 3.2 months vs 4.0 months |
| Bevacizumab ⁴⁸ | Phase II | 46 | Median PFS: 6.9 months Median OS: 12.4 months |
| Ramucicromab ⁴⁹ | Phase II | 42 | Median PFS: 3.9 months Median OS: 14.9 months |
| Everolimus ⁵⁰ | Phase I/II | 20 | Median PFS: 3.8 months Median OS: 8.4 months |
| Pegylated arginine deiminase ⁵¹ | II | 80 | Mean OS: 15.8 months |

Abbreviations: ITT, intent to treat; OS, overall survival; PFS, progression-free survival.

が大きな課題であった。そのため、従来の Milan 基準よりも多くの患者に移植の機会をもたらす、かつ再発率を抑え生存率を担保した基準の策定が模索されている。術前画像診断、術後病理診断において、Milan 基準を超える腫瘍条件でも、術前の AFP が 200ng/ml 以下かつ PIVKA-II が 100mAU/ml 以下であれば、Milan 基準内で AFP と PIVKA-II が高値である症例とほぼ同等の予後が得られることが示されている²⁸⁾。表 2 は現在提唱されている移植基準と、それぞれの 5 年生存率を示した表である (文献 29)より抜粋)。各拡大基準とも、Milan 基準と概ね同等の 75% 前後の 5 年生存率が得られており、適応外症例では Milan 基準よりも低い生存率となっている。すなわち、移植機会の増加に伴い生存率を低下させることなく、Milan 基準では移植適応外となっていた患者の中で、移植により良好な予後が得られる患者群と、予後不良となる患者群の、より鋭敏な選別に成功していると言える。近年では、腫瘍の大きさと数のみでなく、腫瘍の分化度や微小脈管浸潤が肝移植後の予後に影響を与えることが明らかとなり、画像上認識できない微小脈管浸潤の存在を拾い上げる

表 2 肝移植適応基準ごとの成績 (文献(28)より抜粋)

| Criteria | | | 5yr PS(%) |
|----------|-----------------|--------|-----------|
| Milan; | Single, <5cm | within | 77.5 |
| | n<3, s<3cm | beyond | 61.6 |
| Up to 7; | n + size(cm) <7 | within | 76.8 |
| | | beyond | 56.8 |
| Asan; | n<6, s<5cm | within | 75.5 |
| | Vp0 or Vp1 | beyond | 54.7 |
| Kyoto; | n<10, s<5cm | within | 75.2 |
| | PIVKA-II <400 | beyond | 55.6 |
| Tokyo; | 5 x 5 rule | within | 75.9 |
| | | beyond | 55.9 |
| Kyushu; | s <5cm | within | 73.7 |
| | PIVKA-II <300 | beyond | 57.8 |

biomarker の探索や、これらの因子の移植適応基準への応用が模索されている²⁹⁾。

当科の成績

肝細胞癌治療においては、種々の治療法の特徴を十分理解し、一つの治療法にこだわらずに、背景肝の状態に応じ残肝予備能を考慮した柔軟な対応・治療を行うことが肝要である³⁰⁾。

当科の最近の3年間での肝細胞癌切除症例の手術成績では、単純比較はできないが、3年無病再発率は44.4%と、本邦での他施設の最近の報告(5年無病再発率37%)³¹⁾とほぼ同等である。しかし当科の3年全生存率は87.1%と、第18回全国肝癌追跡調査の報告(3年全生存率69.5%)に比して良好である。手術単独の成績は他施設と変わらないが、累積生存率は他施設を上回る。当科では以前より、旭川市内を中心とした道北地域の病院との連携体制を構築している。慢性肝炎、肝硬変患者の定期フォローは消化器内科にて行い、肝細胞癌と診断された症例は、内科的治療と外科的治療を比較して外科治療が適当と判断された場合に、当科への紹介・コンサルトが行われ、あくまで手術は治療オプションの一つとして捉えている。当科にて手術を行い、退院したのちは1-2回の外来受診を経て、再度紹介元の病院の消化器内科、放射線科の協力による定期的フォローを行って頂くことにしている。このように、重厚な診療体制をしるくことによって肝細胞癌患者全てをフォローアップし、集学的治療を行うことが、肝細胞癌治療の予後向上に寄与していると考えている。

終わりに

肝細胞癌治療の最新治療について概説した。個々の治療に関しては未だ試験段階のものが多い。我々は、新たな知見の集積による治療法・治療戦略の開発はもちろん、定期的なフォローと各科横断的な懐の深い診療体制の構築が、肝細胞癌の予後向上につながるものと考えている。

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