

Original Article

Efficacy and safety of tolvaptan in patients with malignant ascites: a phase 2, multicenter, open-label, dose-escalation study

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Abstract

Objective: This phase 2 study examined the efficacy and safety of tolvaptan, an aquaretic drug, in the treatment of ascites associated with cancer.

Methods: In the dose-escalation phase, oral tolvaptan was initiated at a dose of 3.75 mg/day, and the dose was increased daily to 7.5, 15 and 30 mg/day. Dose escalation was terminated once the increase from baseline in the daily urine volume reached 500 ml, at which point the patient proceeded to the maintenance phase of 5–7 days. Improvement of ascites was determined primarily by reduction in body weight and ascitic fluid volume.

Results: The mean change from baseline in body weight was maintained below 0 kg throughout the study. The mean change ($\pm$ standard deviation) from baseline in ascitic fluid volume at the end of treatment (EOT) was 237.45 ± 868.14 ml in 33 evaluable patients. Although an increase from baseline in ascitic fluid volume at the EOT was observed in 23 of 33 patients (maximum: 1589.3 ml, minimum: 3.83 ml), a reduction in ascitic fluid volume was observed in the remaining 10 patients (maximum: -2304.3 ml, minimum: -27.5 ml). The common treatment-emergent adverse events included vomiting (5 of 43 patients, 11.6%), abdominal distension, constipation, thirst, blood osmolality increased and renal impairment (3 of 43 patients, 7.0% each).

Conclusions: Tolvaptan seemed to have no definitive effect on reducing ascites; however, it might be effective in at least some cancer patients. No new safety concerns were identified at doses of 3.75–30 mg/day.

Key words: malignant ascites, ascitic fluid, carcinoma, safety, tolvaptan

Introduction

Malignant ascites is the accumulation of fluid in the abdominal cavity resulting from carcinoma and accounts for ~10% of all cases of ascites (1,2). It can be caused by a wide variety of cancer types, including ovarian, breast, colon, gastric and pancreatic cancers (3), and more than 20% of malignant ascites are associated with tumors of unknown primary origin (4).

The development of malignant ascites occurs through the increased production and decreased absorption of ascitic fluid. The increased production of ascitic fluid is mediated by peritoneal angiogenesis and augmented vascular permeability that are stimulated by tumor cell-derived growth factors, such as interleukin-6 and vascular endothelial growth factor (2). In liver cancer and hepatic metastases, portal hypertension, enhanced production of hepatic lymph and hyperpermeability of portal branches are also responsible for fluid accumulation (2). On the other hand, the decreased absorption of ascitic fluid occurs primarily via the obstruction of lymphatic vessels by tumor cells (2).

Diuretics, including loop diuretics and anti-aldosterone medications, are commonly used for the treatment of fluid retention associated with cancer (3,5,6). The administration of such diuretics is usually initiated at a low dose, and the dose is then gradually increased. However, increasing the dose of loop diuretics often leads to hyponatremia and hypokalemia. While hypokalemia can be alleviated by the concomitant use of anti-aldosterone medications and potassium preparations, it is difficult to prevent or treat hyponatremia. Furthermore, the effect of diuretics is known to be diminished by the progression of the underlying cancer itself and/or malignant ascites. It has been reported that 61–86% of physicians use diuretics for the treatment of malignant ascites, but only 45% consider them to be clinically effective (5,6). Another therapeutic option is the drainage of ascitic fluid by paracentesis, which is resorted to particularly in the case of refractory malignant ascites (3,7). Although the effectiveness of large-volume paracentesis has been established since the 1980s, a risk of hypotension and circulatory failure, including decreased renal perfusion, exists (7).

Tolvaptan is a non-peptide arginine vasopressin V2 receptor antagonist developed by Otsuka Pharmaceutical Co., Ltd. (8). This oral agent suppresses water resorption at the kidney collecting duct, thereby promoting the excretion of water. Tolvaptan is currently approved in the USA and other countries for the treatment of hyponatremia in heart failure and the syndrome of inappropriate secretion of antidiuretic hormone. In Japan and some other Asian countries, it is approved for the treatment of fluid retention in heart failure and hepatic cirrhosis in patients who are refractory to diuretics. Furthermore, in Japan, the European Union, the USA and some other countries, tolvaptan has received approval for slowing the progression of autosomal dominant polycystic kidney disease.

Unlike conventional diuretics, tolvaptan is an aquaretic agent, i.e. it enhances the removal of free water without the excretion of electrolytes, including sodium (9). Thus, it has the potential to treat fluid retention without causing or exacerbating hyponatremia, which is frequently observed in cancer patients (10). Indeed, it has been demonstrated that tolvaptan is effective in correcting hyponatremia in patients with solid tumors and lung cancer (11,12). Meanwhile, it has been reported that tolvaptan significantly alleviated abdominal distension in 10 patients with heart failure and malignancy accompanied by ascites (13). On the other hand, it is important to monitor serum sodium concentration while using tolvaptan because it can induce hyponatremia owing to its mechanism of action (14).

These observations suggest that tolvaptan could potentially be used as a therapeutic agent for the management of ascites associated with cancer. However, there have been few studies that specifically investigated the effect of tolvaptan on malignant ascites.

Accordingly, we conducted a multicenter, open-label, dose-escalation study to investigate the efficacy and safety of tolvaptan in patients with fluid retention associated with carcinoma.

Materials and methods

This study was conducted from November 2012 to November 2013 at 30 centers in Japan. Written informed consent was obtained from all participants before the initiation of study-related activities. The study was approved by the institutional review boards of all participating sites and was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Pharmaceutical Affairs Law and the Ministerial Ordinance on Good Clinical Practice for Drugs [Ministry of Health and Welfare (Japan) Ordinance No. 28, dated 27 March 1997]. The study is registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov/ct2/show/study?term=NCT01684202&rank=1) (NCT01684202).

Study design and treatment

This phase 2, multicenter, open-label study comprised a screening period, a pretreatment period, a treatment period and a post-treatment period (Supplementary Fig. S1). The treatment period consisted of a dose-escalation phase and a maintenance phase. Patients were admitted to a hospital and monitored from the day before the pretreatment period to the last day of the post-treatment period. Tolvaptan was orally administered to the patients once daily after breakfast. In the dose-escalation phase, tolvaptan was initiated at a dose of 3.75 mg on day 1, and the dose was sequentially increased to 7.5 mg on day 2, 15 mg on day 3 and 30 mg on day 4. Dose increase was allowed only if the increase in daily urine volume (dUV) from the last day of the pretreatment period was <500 ml (i.e. the effect of tolvaptan was judged to be inadequate). Once the increase in dUV reached 500 ml, the dose was fixed, and the patient proceeded to the maintenance phase in which tolvaptan was administered at the same dose for 5–7 days. A dUV increase of <500 ml was chosen as the criterion for dose increase because the maximum daily volume of ascitic fluid translocated into peritoneal capillaries is estimated to be 500–900 ml (15). In addition, a *post hoc* analysis in patients with liver cirrhosis suggests that a dUV increase of <500 ml can be interpreted as a sign of a poor response to tolvaptan (16) and doubling the dose in such low responders would be unlikely to cause any serious safety concerns, including dehydration due to an acute increase in urine volume.

Conventional diuretics could not be administered to the patient population in this study owing to the known side effect of hyponatremia, and diuretics were not expected to be effective owing to an increased fluid retention rate associated with malignant ascites. Therefore, concomitant use of diuretics, which is required with the use of tolvaptan for fluid retention in patients with heart failure and hepatic cirrhosis, was not mandatory in this study. However, considering safety concerns such as hyponatremia due to tolvaptan treatment, measurement of serum sodium concentration was planned at the following time points to ensure patient safety: 4–6 hours, 8–12 hours and 22–24 hours after the daily dosing of the study drug in the dose-escalation phase; 1 day during days 2–4 in the maintenance phase; and before breakfast on day 1 after the final dosing. A provision was made to discontinue the study drug if

the serum sodium concentration increased by 12 mEq/l or more during the dose-escalation phase or by 155 mEq/l or more during the treatment period, and the study was conducted in such a way that the investigator could respond promptly when safety issues occurred.

Concomitant use of other oral diuretics was permitted only if they had been regularly used prior to the study, but no change in the dose and regimen was allowed during the pretreatment and treatment periods. Chemotherapy was allowed only if the same regimen was to be continued after completing at least 1 cycle before the start of the pretreatment period. Prohibited concomitant medications and therapies included diuretic injection, albumin preparations, paracentesis, thoracentesis, peritoneovenous shunt and cancer treatment (surgery, radiation and intraperitoneal chemotherapy).

Ascites were judged to be exudative if the concentration difference in albumin between the serum and ascites (serum value – ascites value) was <1.1 g/dl and transudative if it was 1.1 g/dl or more. However, in patients whose ascites types were already determined by abdominal paracentesis before the start of the study, measurement using paracentesis was not required in this study to avoid invasive risk to the patients, and the method for determining the type of the ascites was left to the investigator's judgment.

Inclusion and exclusion criteria

Patients aged between 20 and 80 years with malignant ascites and histologically or cytologically proven cancer were enrolled. Patients were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, with survival expectancy of at least 3 months after obtaining consent. Only inpatients or patients who could be hospitalized for the study were eligible. Patients, together with their partners, were required to practice contraceptive methods from the date of consent until 4 weeks after the final administration of the study drug. Patients were excluded if they had any of the following complications or symptoms: deep vein thrombosis; intestinal obstruction or intestinal edema with symptoms similar to intestinal obstruction; hepatic cirrhosis; anuria; impaired urination due to urinary tract stricture, urinary calculus, tumor in the urinary tract or other causes; continuing symptoms of diarrhea or vomiting; and infection requiring systemic treatment. Other major exclusion criteria included a history of cerebrovascular disorder or coronary disease within 4 weeks prior to the start of the pretreatment period; a history of hypersensitivity to analogous compounds, such as mozavaptan hydrochloride; a history of gastrectomy or enterectomy to an extent that absorption of oral medication was affected, abnormal laboratory values (platelet count <75 000/mm³, hemoglobin <8.0 g/dl, neutrophil count <1000/mm³, total bilirubin >4.0 mg/dl, serum creatinine >3.0 mg/dl, serum sodium >147 mEq/l or serum potassium >5.5 mEq/l), previous treatment with albumin products or blood products containing albumin within 1 week prior to the start of the pretreatment period; and previous surgical treatment or radiation therapy for cancer within 4 weeks prior to the start of the pretreatment period. Patients in whom it was difficult to evaluate the efficacy and safety of the study drug owing to the effects of chemotherapy (e.g. improvement in malignant ascites due to chemotherapy or edema due to a side effect of chemotherapy), as judged by the investigator, were excluded from the study.

The reasons for study discontinuation are presented in [Supplementary Table S1](#).

Efficacy analyses

Efficacy of tolvaptan for malignant ascites was evaluated based on the changes from baseline in body weight as well as ascitic fluid volume determined by computed tomography (CT). Other efficacy endpoints included clinical outcomes for ascites retention assessed by echogram, outcomes for ascites-related clinical symptoms (abdominal distension, decreased appetite, malaise, sensation of pressure in recumbent position, feeling of dyspnea and general condition), change from baseline in abdominal circumference, outcomes for lower limb edema, outcomes for pleural effusion assessed by echogram and quality of life based on the 5-level version of EuroQol 5-dimensional questionnaire (EQ-5D-5L).

Body weight was measured every morning after urination but before breakfast throughout the pretreatment and treatment periods. The assessment of ascitic fluid volume using CT was conducted once 1–3 days prior to the dose-escalation phase and once on the last day of the maintenance phase. CT data were centrally assessed by Perceptive Informatics, Inc. (New Jersey, USA), an image analysis facility. The clinical outcomes for ascites retention and ascites-related symptoms were classified as 'resolved', 'improved', 'unchanged' or 'exacerbated'. The clinical outcomes for pleural effusion were classified as 'resolved', 'unchanged' or 'exacerbated'. Lower limb edema was rated on a 4-point scale [0: none (no pitting), 1: mild (mild pitting), 2: moderate (moderate pitting), 3: severe (apparent edema)] and was classified as 'markedly improved', 'improved', 'unchanged' or 'exacerbated'.

Pharmacological analyses

Pharmacological assessments included the monitoring of daily water intake (dWI), dUV, serum sodium and potassium concentrations, and serum osmolality. Urine and blood samples were collected before breakfast. dWI was defined as the total volume of fluid (drinking water, infusion and beverages of all kinds) consumed over 24 hours following predose urination.

Safety analyses

All treatment-emergent adverse events (TEAEs) were recorded. All patients underwent laboratory analyses (hematology, blood chemistry and urine), vital signs assessment, physical examination and 12-lead electrocardiogram.

Statistical analyses

No statistical calculation was done in determining the sample size because this trial was intended as an exploratory study. Safety analyses were based on the safety analysis set (SS), which included all patients who received ≥1 dose of the study drug. Efficacy analyses were based on the full analysis set (FAS), which included all patients who received ≥1 dose of the study drug and had ≥1 post-dose efficacy measurement. No statistical tests were performed for any of the efficacy outcomes. Descriptive statistics [mean and standard deviation (SD)] were determined for all continuous data. Efficacy and safety results were summarized for all patients as well as for each dose group (i.e. the 3.75, 7.5, 15 or 30 mg group according to the fixed dose used in the maintenance phase). For all variables, data obtained immediately before the initiation of the dose-escalation phase were defined as baseline data unless otherwise noted. Data obtained on the final dosing day or 1 day after the final dosing day were defined as data at the EOT. The correlation between the change from baseline in body weight and in ascitic fluid volume at the EOT

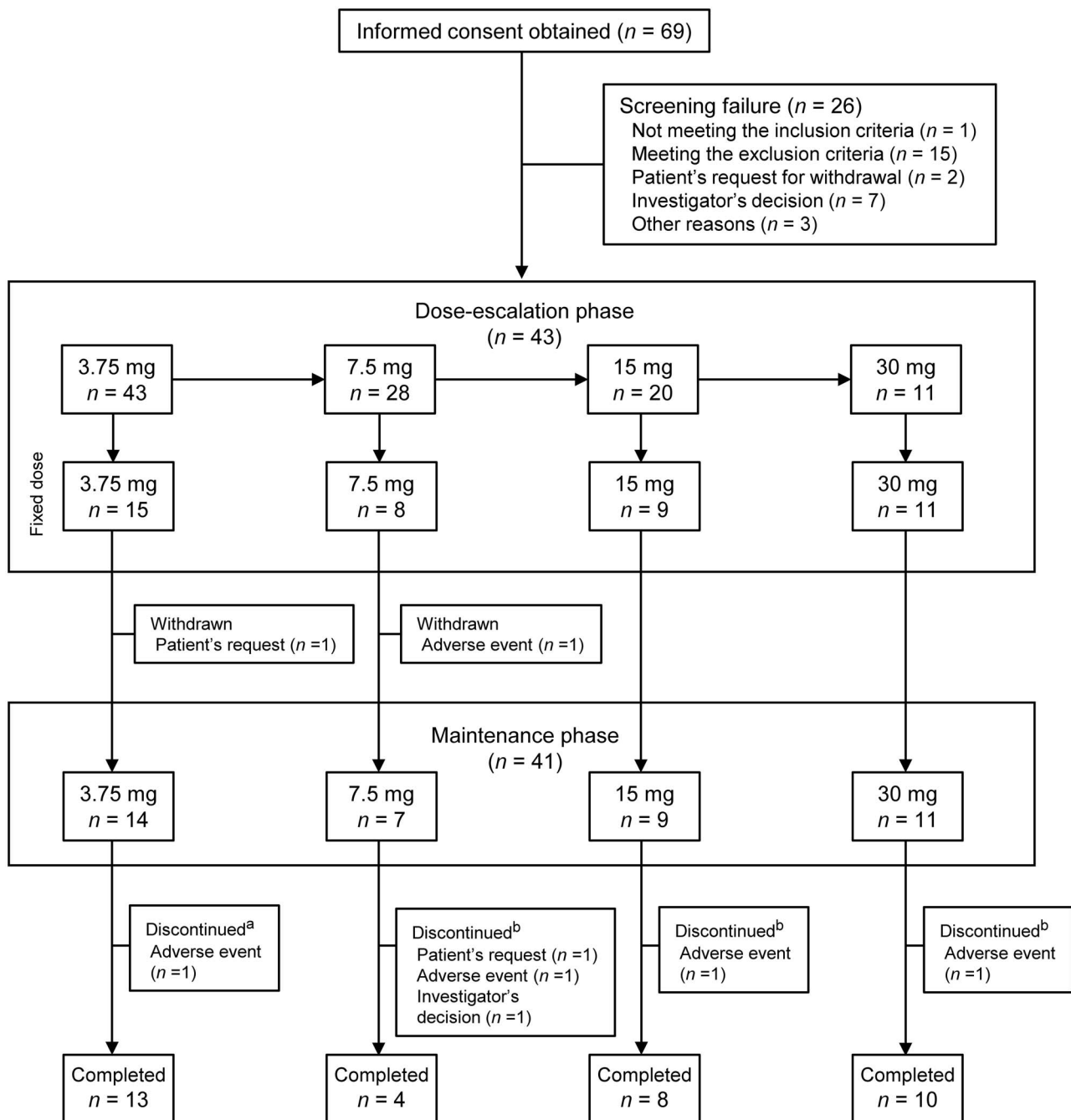


Figure 1. Flow chart of patient disposition. a, post-treatment period; b, maintenance phase.

was determined using Pearson's correlation coefficient. TEAEs were coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities version 16.1.

Results

Patient disposition and characteristics

A total of 69 patients with malignant ascites were enrolled at 30 clinical sites in Japan, and 43 patients were judged to be eligible for the study. Among the 43 patients who started the dose-escalation phase, 41 proceeded to the maintenance phase and received tolvaptan

at a fixed dose of 3.75 mg (14 patients), 7.5 mg (7 patients), 15 mg (9 patients) or 30 mg (11 patients) (Fig. 1). Of the 41 patients, 35 completed the study. The SS and FAS consisted of 43 and 40 patients, respectively. Three patients were excluded from the FAS because no efficacy measurements after the initiation of study treatment were obtained. During the dose-escalation phase, one patient was withdrawn due to adverse events, while another was withdrawn at his/her own request. During the maintenance phase, five patients discontinued treatment: three because of adverse events, one at the patient's own request and one owing to the investigator's decision. In addition, one patient discontinued treatment during the post-treatment period due to adverse events.

Table 1. Baseline demographic and clinical characteristics of patients

Parameter	Total (n = 40)
Sex, n (%)	
Male	16 (40.0)
Female	24 (60.0)
Age (years)	
Mean $\pm$ SD	65.3 $\pm$ 8.8
Body weight (kg)	
Mean $\pm$ SD	51.49 $\pm$ 11.20
ECOG performance status, n (%)	
0	7 (17.5)
1	16 (40.0)
2	16 (40.0)
3	1 (2.5)
Underlying cancer, n (%)	
Gastric	15 (37.5)
Pancreatic	9 (22.5)
Colon	5 (12.5)
Biliary tract	3 (7.5)
Ovarian	3 (7.5)
Uterus	1 (2.5)
Other	4 (10.0)
Ascites type, n (%)	
Exudative	15 (37.5)
Transudative	23 (57.5)
Ascites volume (ml)	
Mean $\pm$ SD	3336.3 $\pm$ 2510.5
Ascites-related symptoms, n (%)	
Abdominal distension	35 (87.5)
Decreased appetite	24 (60.0)
Malaise	27 (67.5)
Sensation of pressure in recumbent position	19 (47.5)
Feeling of dyspnea	11 (27.5)
Abdominal circumference (cm)	
Mean $\pm$ SD	82.80 $\pm$ 10.45
Lower limb edema, n (%)	
None	18 (45.0)
Mild	13 (32.5)
Moderate	3 (7.5)
Severe	6 (15.0)
Concomitant medications, n (%)	
Diuretics ^{a,b}	22 (55.0)
Loop diuretic	21 (52.5)
Thiazide diuretic	1 (2.5)
Anti-aldosterone drug	15 (37.5)
Chemotherapy ^c	11 (27.5)

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group.

^aConcomitant medications received from the start date to the end of treatment.^bPatients may have received more than one concomitant diuretic.^cConcomitant therapies received from 4 weeks prior to the date of informed consent to the end of treatment.

Patient characteristics are shown in Table 1. Of the 40 patients included in the FAS, 24 were female (60.0%) and the mean age was 65.3 years. The most common underlying cancer type was gastric cancer (15 patients, 37.5%), followed by pancreatic cancer (9 patients, 22.5%) and colon cancer (5 patients, 12.5%). Most patients had an ECOG performance status of 1 or 2 (16 patients, 40.0% each). In terms of ascites types, 23 patients (57.5%) had

transudative ascites, while 15 (37.5%) had exudative ascites. Clinical issues regarding previous use of diuretics included 'no efficacy can be expected' (14 patients, 35.0%) and 'electrolyte abnormalities' (6 patients, 15.0%). The most common symptom associated with ascites was abdominal distension (35 patients, 87.5%), followed by malaise (27 patients, 67.5%).

Efficacy

Overall, a reduction in body weight was observed from day 1 of tolvaptan treatment, and the mean change from baseline was maintained below 0 kg throughout the study (Fig. 2). The mean change ($\pm$ SD) from baseline in body weight at the EOT was -0.35 ± 2.05 kg in all patients, -0.69 ± 2.51 kg in the 3.75 mg group, -0.34 ± 1.99 kg in the 7.5 mg group, -1.13 ± 1.62 kg in the 15 mg group and 0.70 ± 1.56 kg in the 30 mg group.

The mean change ($\pm$ SD) from baseline in ascitic fluid volume at the EOT was 237.45 ± 868.14 ml [maximum (max): 1589.3 ml, minimum (min): -2304.3 ml] in all patients (33 patients), -77.20 ± 982.19 ml in the 3.75 mg group, 513.97 ± 653.30 ml in the 7.5 mg group, 153.72 ± 993.63 ml in the 15 mg group and 539.93 ± 659.36 ml in the 30 mg group (Fig. 3). Although an increase from baseline in ascitic fluid volume at the EOT was observed in 23 of 33 patients (max: 1589.3 ml, min: 3.83 ml), a reduction in ascitic fluid volume was observed in the remaining 10 patients (max: -2304.3 ml, min: -27.5 ml) (Supplementary Table S2). The Pearson's correlation coefficient between the change from baseline in body weight and that in ascitic fluid volume at the EOT in the 33 patients was 0.60739 (Supplementary Fig. S2). The correlation coefficient between ascites types and changes in body weight and in ascitic fluid volume were 0.28599 and 0.20820, respectively (Supplementary Figs S3 and S4).

As a *post hoc* analysis, changes in body weight and ascitic fluid volume were examined in patients who had a dUV increase of ≥ 500 ml (27 patients) or 700 ml (17 patients) on the last day of the dose-escalation phase. The mean change ($\pm$ SD) from baseline in body weight at the EOT was -0.68 ± 2.18 kg in patients with a dUV of ≥ 500 ml and -1.08 ± 2.39 kg in patients with a dUV of ≥ 700 ml (Supplementary Fig. S5A). The mean change ($\pm$ SD) from baseline in ascitic fluid volume at the EOT was 123.63 ± 933.89 ml in patients with a dUV of ≥ 500 ml and -46.89 ± 1001.94 ml in patients with a dUV of ≥ 700 ml (Supplementary Fig. S5B). In general, patients with a greater dUV exhibited a greater reduction in both body weight and ascitic fluid volume at the EOT.

Based on the investigator's assessment, ascites was resolved or improved in 11 of 35 patients (31.4%) at the EOT, while it was exacerbated in 6 patients (17.1%) (Supplementary Table S3). Among ascites-related symptoms, abdominal distension, sensation of pressure in recumbent position, feeling of dyspnea and general condition were resolved or improved in more patients in the treatment period than in the pretreatment period (Supplementary Table S4).

As for abdominal circumference, there was no obvious reduction or increase from baseline at the EOT. Lower limb edema was improved (defined as a decrease of ≥ 1 point in the severity scale) at the EOT in 5 of 23 patients (21.7%), and it was resolved in 3 patients (13.0%). Pleural effusion was resolved in 2 of 17 patients (11.8%), while it was exacerbated in 1 patient (5.9%). No apparent improvements in any dimension of EQ-5D-5L (Supplementary Table S5) and ECOG performance status (Supplementary Table S6) were observed.

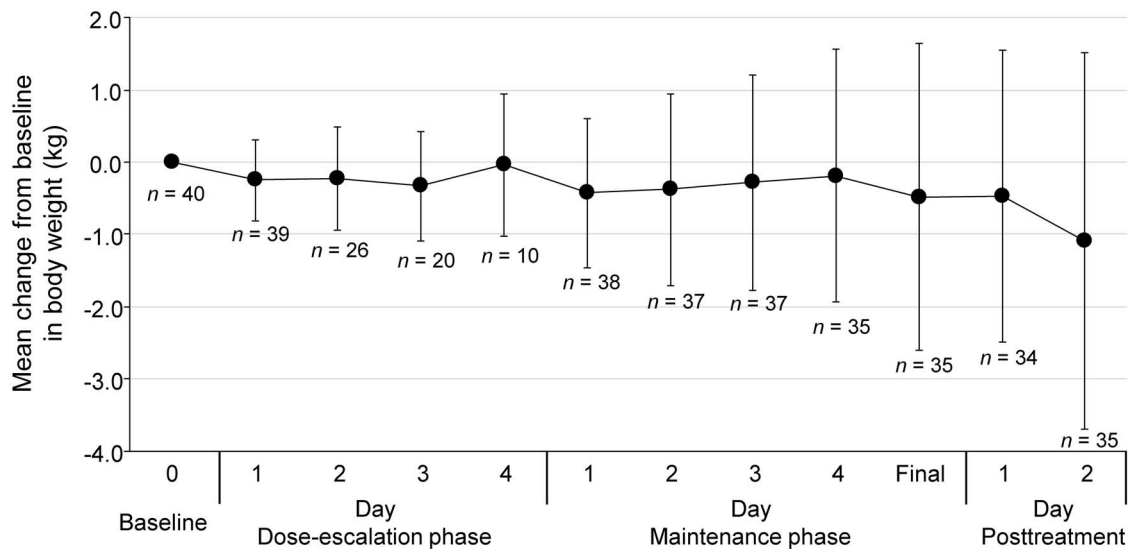


Figure 2. Time-course of change from baseline in body weight in all patients after initiation of tolcapitan. Data are expressed as mean $\pm$ standard deviation. In this study, a maintenance phase of 5–7 days was established. Since the maintenance phase is different for each patient, the final observation day in the maintenance phase for each patient is indicated as 'Final'. 'Final' for the timepoint includes the data obtained on the final observation day (day 5, 6 or 7) in the maintenance phase for each patient. Since only a small number of patients had an observation period of 6 or 7 days, the day 5 data of patients with an observation period of 6 days and the day 5 or 6 data of patients with an observation period of 7 days are not shown; rather, the day 6 and day 7 data in each observation period are shown as 'Final'. Therefore, in this figure, the data from day 1 to day 4 and 'Final', including data obtained on day 5, 6 or 7, are shown.

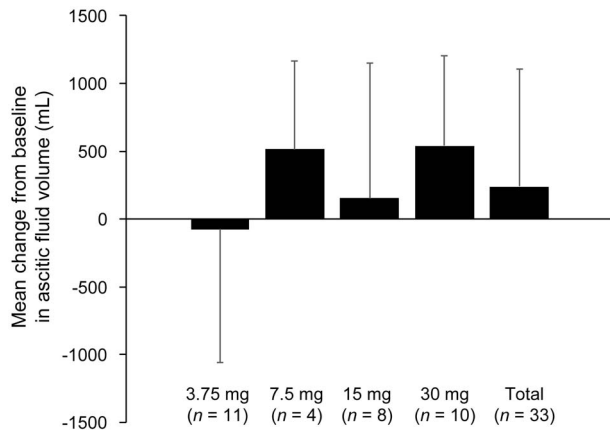


Figure 3. Mean change from baseline in ascitic fluid volume at the end of treatment in all patients as well as in each dose group. Data are expressed as mean $\pm$ standard deviation.

Pharmacological action

Overall, an increase in dUV was observed from day 1 of the dose-escalation phase, and the mean change from baseline was maintained >200 ml throughout the study (Fig. 4). The mean changes ($\pm$ SD) from baseline in dUV and dWI at the EOT in all patients were 240.3 ± 444.7 ml and 155.1 ± 448.5 ml, respectively. The mean change ($\pm$ SD) from baseline in serum sodium concentration at the EOT in all patients was 2.4 ± 2.2 mEq/l, and no dose-dependent increase was observed. The mean change ($\pm$ SD) from baseline in serum sodium concentration at the EOT in patients with baseline serum sodium concentrations <135 mEq/l was 3.1 ± 2.3 mEq/l in all patients, 3.4 ± 1.5 mEq/l in the 3.75 mg group, 3.3 ± 1.7 mEq/l in the 7.5 mg group, 3.0 ± 1.4 mEq/l in the 15 mg group and 2.8 ± 3.8 mEq/l in the 30 mg group. An increase in serum sodium concentration was also observed in patients with hyponatremia

(serum sodium level <135 mEq/l) in all dose groups. The mean change ($\pm$ SD) from baseline in serum potassium concentration at the EOT in all patients was -0.07 ± 0.44 mEq/L. The mean change ($\pm$ SD) from baseline in serum osmolality at the EOT in all patients was 6.1 ± 5.3 mOsm/l (Supplementary Table S7).

Safety

In the SS (43 patients), TEAEs were observed in 32 patients (74.4%) during the study (Table 2). TEAEs reported in $\geq 5\%$ of patients were vomiting (5 patients, 11.6%), abdominal distension, constipation, thirst, blood osmolality increased and renal impairment (3 patients, 7.0% each). Drug-related TEAEs were reported in 14 patients (32.6%). Drug-related TEAEs reported in $\geq 5\%$ of patients were thirst, blood osmolality increased and renal impairment (3 patients, 7.0% each).

TEAEs leading to discontinuation of the study drug were observed in four patients (9.3%): renal impairment in two patients, bile duct cancer in one patient and pelvic venous thrombosis in one patient. Of these TEAEs, a causal relationship between renal impairment and the study drug could not be ruled out. Similarly, a causal relationship between bile duct cancer and tolcapitan could not be ruled out because of an overlap between the period of taking tolcapitan and the exacerbation period of the bile duct cancer and the possibility that the underlying cancer might have progressed owing to dehydration caused by the diuretic effect of tolcapitan. Meanwhile, a causal relationship between pelvic venous thrombosis and the study drug was ruled out.

No deaths were reported during the study, but two patients died during the follow-up period. One patient had an exacerbation of bile duct cancer, for which a causal relationship to the study drug could not be ruled out. The other patient had an exacerbation of gastric cancer, which was a serious TEAE, but any causal relationship between this event and tolcapitan was ruled out. With regard to other

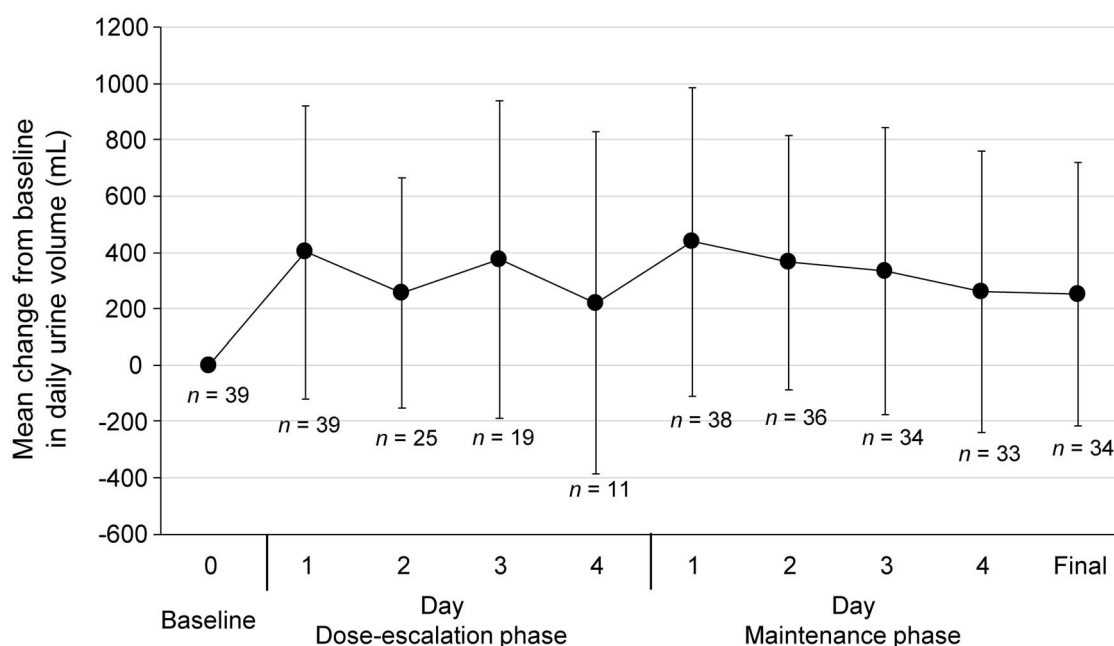


Figure 4. Time-course of change from baseline in daily urine volume in all patients after initiation of tolvaptan. Data are expressed as mean $\pm$ standard deviation. In this study, a maintenance phase of 5–7 days was established. Since the maintenance phase is different for each patient, the final observation day in the maintenance phase for each patient is indicated as 'Final'. 'Final' for the timepoint includes the data obtained on the final observation day (day 5, 6 or 7) in the maintenance phase for each patient. Since only a small number of patients had an observation period of 6 or 7 days, the day 5 data of patients with an observation period of 6 days and the day 5 or 6 data of patients with an observation period of 7 days are not shown; rather, the day 6 and day 7 data in each observation period are shown as 'Final'. Therefore, in this figure, the data from day 1 to day 4 and 'Final', including data obtained on day 5, 6 or 7, are shown.

Table 2. Summary of treatment-emergent adverse events

	3.75 mg (n = 15)	7.5 mg (n = 8)	15 mg (n = 9)	30 mg (n = 11)	Total (n = 43)
Any TEAE	8 (53.3)	6 (75.0)	8 (88.9)	10 (90.9)	32 (74.4)
TEAEs reported in $\geq 5\%$ of all patients					
Vomiting	2 (13.3)	0 (0.0)	2 (22.2)	1 (9.1)	5 (11.6)
Abdominal distension	1 (6.7)	0 (0.0)	1 (11.1)	1 (9.1)	3 (7.0)
Constipation	0 (0.0)	1 (12.5)	0 (0.0)	2 (18.2)	3 (7.0)
Thirst	1 (6.7)	0 (0.0)	1 (11.1)	1 (9.1)	3 (7.0)
Blood osmolarity increased	1 (6.7)	1 (12.5)	0 (0.0)	1 (9.1)	3 (7.0)
Renal impairment	0 (0.0)	0 (0.0)	1 (11.1)	2 (18.2)	3 (7.0)
TEAEs leading to discontinuation					
Any	0 (0.0)	2 (25.0)	1 (11.1)	1 (9.1)	4 (9.3)
Bile duct cancer	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (2.3)
Renal impairment	0 (0.0)	0 (0.0)	1 (11.1)	1 (9.1)	2 (4.7)
Pelvic venous thrombosis	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (2.3)

Data are expressed as n (%) of patients. TEAE, treatment-emergent adverse event.

serious TEAEs, one patient's general condition deteriorated, which was initially considered to be non-serious, and a causal relationship between this event and the study drug could not be ruled out.

No clinically relevant changes were observed in laboratory values, vital signs, physical examination or 12-lead electrocardiogram. No patient exhibited an increase in serum sodium concentration by ≥ 12 mEq/l during the dose-escalation phase. In addition, no patient had a serum sodium concentration ≥ 155 mEq/l from the start of the treatment period to the day following the final dosing day. The

measured value was in the range of 118–146 mEq/l, which was within the standard value range. There were no clinically problematic changes in circulating plasma volume.

Discussion

This exploratory study represents the first trial that aimed to ascertain the efficacy and safety of tolvaptan in patients with malignant

ascites. Although the present study could not establish that tolvaptan had a therapeutic benefit in these patients, we were able to obtain useful information for future studies.

During a period of up to 11 days of treatment with tolvaptan, there was a numerical decrease in body weight on an average in all patients. The mean changes from baseline in body weight at the EOT were negative values in all dose groups except in the 30 mg group. It should be noted that 30 mg was the maximum daily dose in our dose-escalation design and a further dose increase owing to an inadequate response was not allowed. Thus, the 30 mg group intrinsically included 'low responders' who showed only a marginal response to tolvaptan, as indicated by a dUV increase of <500 ml.

Although the mean change from baseline in ascitic fluid volume showed a numerical increase in all patients, 10 patients (30.3%) exhibited a reduction in the fluid volume, with an average of ~700 ml at the EOT. This percentage of responders is not inconsequential in light of a previous systematic review, which found that at most 43% of patients experienced relief from ascites (3). Furthermore, ascites associated with cancer is usually intractable and the fluid volume continuously increases as the cancer progresses. Given this clinical challenge, the finding that tolvaptan reduced ascites volume in at least some patients may indicate clinical significance.

Our *post hoc* analysis revealed that patients who had a dUV increase of ≥ 700 ml on the last day of the dose-escalation phase responded better to tolvaptan at the EOT than those with a dUV increase of ≥ 500 ml. This observation suggests that the effect of tolvaptan as an anti-ascites agent may be correlated with its effect as a diuretic and that dUV could possibly be used as a potential predictor of clinical outcome in patients with malignant ascites.

TEAEs occurred in 74.4% of patients during this study, which is comparable to the percentage (82%) previously reported in a 14-day administration study of tolvaptan in patients with hepatic edema (17). The drug-related TEAEs observed in the present study included thirst and blood osmolarity increased, both of which are related to the pharmacological action (aquaresis) of tolvaptan (9).

Hyponatremia, which frequently occurs in cancer patients through a variety of mechanisms (10,18,19), can be exacerbated by the use of conventional loop diuretics due to their natriuretic effect (20,21). However, tolvaptan improved hyponatremia in patients who had a low serum sodium concentration (<135 mEq/l) at baseline, suggesting that, unlike natriuretic drugs, the aquaretic tolvaptan could be safely used for the treatment of malignant ascites without increasing the risk of electrolyte imbalance.

Thrombosis is another concern when treating malignant ascites with diuretics. In general, patients with cancer are at a high risk of thrombosis, including deep vein thrombosis, due to intravascular dehydration associated with ascitic fluid accumulation as well as enhanced coagulation mediated by tumor cells (22). This risk may be further increased by the diuretic effect of tolvaptan. However, only one patient in the 7.5 mg group developed thrombosis (pelvic venous thrombosis), which was not drug-related, and no trend towards an increased risk of thrombosis was identified.

Our study has several limitations. First, the present study was not a controlled trial; thus, it is difficult to distinguish the effect of tolvaptan from outcomes caused by other factors, such as natural progression of underlying diseases and use of concomitant diuretics or therapies. Second, the sample size was small since this trial was intended as an exploratory study, making it difficult to draw robust conclusions in terms of the efficacy of tolvaptan. Lastly, there could

be room for improvement in the dose-escalation scheme. In this study, dose increases were terminated once the increase in dUV from baseline reached 500 ml. This threshold was selected mainly as a safety precaution as there was a possibility that a strong diuretic effect might increase the risk of thrombosis. However, the *post hoc* analysis showed a greater reduction in both body weight and ascitic fluid volume in patients who had a dUV increase of ≥ 700 ml during the dose-escalation phase. Thus, a threshold higher than 500 ml should also be taken into consideration if another study is conducted in the future.

In conclusion, no new or unexpected safety concerns were identified with tolvaptan at doses of 3.75–30 mg/day in patients with malignant ascites. Although our study found no definitive evidence that tolvaptan is effective in reducing ascites volume, the efficacy data suggested that there may exist a specific patient population who can benefit from tolvaptan treatment.

Supplementary material

Supplementary material can be found at *JJCO* online.

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Conflict of interest statement

T.K. reports personal fees from Otsuka Pharmaceutical Co., Ltd for the work under consideration for publication. He reports grants from Yakult Honsha Co., Ltd and grants and personal fees from Chugai Pharmaceutical Co., Ltd, ONO Pharmaceutical Co., Ltd, Eli Lilly Japan Co., Ltd and Bayer Yakuhin, Ltd. He also reports personal fees from Merck KGaA, MSD Co., Ltd, Sanofi Co., Ltd, Takeda Pharmaceutical Co., Ltd and Taiho Pharmaceutical Co., Ltd, outside the submitted work. T.S. reports personal fees from Otsuka Pharmaceutical Co., Ltd. for the work under consideration

for publication. Y.M., Y.K. and K.U. are full-time employees of Otsuka Pharmaceutical Co., Ltd.

Authors' contributions

T.K., T.S., Y.M. and Y.K. conceived and designed the study and contributed to data acquisition. Y.M. and Y.K. analyzed the data. T.K., T.S., Y.M., Y.K. and K.U. contributed to the interpretation of the data and critically reviewed and revised the manuscript. All authors approved the final manuscript for submission.

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