Safety and efficacy of trifluridine/tipiracil in treatment of patients with advanced gastric cancer having ascites

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Abstract

Background: Trifluridine/tipiracil (FTD/TPI) is an oral chemotherapy comprising a thymidine-based nucleoside analog and a thymidine phosphorylase inhibitor. The FTD/TPI versus placebo in patients with heavily pretreated metastatic gastric cancer trial showed that FTD/TPI is effective with manageable toxicity in these patients. However, data on the effect of FTD/TPI on patients with advanced gastric cancer (AGC) having ascites are limited.

Methods: We retrospectively collected and analyzed the clinicopathologic data of patients with AGC who had received FTD/TPI monotherapy in our institutions from September 2019 to July 2021.

Results: A total of 44 patients were included in this study. The median age was 71 (range, 37–85) years, 22 patients were men, the numbers of patients with Eastern Cooperative Oncology Group performance status scores 0, 1, and 2 were 8, 32, and 4, respectively, and 25 patients had diffuse-type histology. A total of 25 patients had ascites, among whom 13 had massive ascites. The response rate and disease control rate (DCR) were 2% and 41%, respectively. The median progression-free survival was 2.4 months and median overall survival (OS) was 5.8 months. Patients with ascites exhibited significantly shorter OS (8.6 vs. 4.7 months, P=0.0406) than those without ascites, and DCR (68% vs. 20%, P=0.0012) was significantly worse in patients with ascites. There was no significant difference in the frequency of occurrence of adverse events of grade 3 or higher between patients with and without ascites.

Conclusion:

FTD/TPI has a moderate, although inadequate, effect on patients with AGC having ascites.

Introduction

Gastric cancer is the third leading cause of cancer-related death and the fifth most common malignancy diagnosed worldwide [1] and systemic chemotherapy is the standard treatment for unresectable, metastatic gastric cancer. The results of the nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with human epidermal growth factor receptor 2-negative, untreated, unresectable advanced or recurrent gastric or gastro-esophageal junction cancer (ATTRACTION-4) and first-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-esophageal junction, and esophageal adenocarcinoma (CHECKMATE649) trials led to the development of a combination of chemotherapy and nivolumab as the new standard regimen for first-line treatment of advanced gastric cancer (AGC) [2, 3]. In cases where third-line treatment is possible, trifluridine/tipiracil (FTD/TPI) or CPT-11 based regimens may be considered. FTD/TPI is an oral therapy comprising the thymidine analog trifluridine and tipiracil, which prevents trifluridine degradation [4]. The FTD/TPI versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS) trial, which is a phase 3 study involving patients with AGC treated with two or more regimens, showed that compared with the placebo, FTD/TPI results in significant rise of progression-free survival (PFS) and overall survival (OS) [5].

Currently, FTD/TPI is approved in the United States, Europe, and Japan for patients previously treated for AGC.

However, in actual clinical practice, many patients with AGC exhibit severe conditions, such as ascites, which is rare among those registered in clinical trials. While the TAGS study comprises data on patients with peritoneal dissemination, information on those with ascites is absent. To the best of our knowledge, this is the first study to evaluated the efficacy and safety of FTD/TPI therapy for patients with AGC having ascites. Therefore, we retrospectively evaluated the efficacy and safety of FTD/TPI therapy for patients with AGC having ascites.

Methods

Patients

We reviewed the medical records of consecutive patients with AGC who were treated with FTD/TPI between January 2019 and July 2021 at the Kobe City Medical Center General Hospital, Himeji Red Cross Hospital, and Osaka Red Cross Hospital, Japan. The inclusion criteria were as follows: (1) unresectable gastric cancer, (2) histologically proven gastric adenocarcinoma, (3) refractory or intolerant to at least two prior regimens, (4) at least one evaluable lesion.

Treatment

The patients received oral FTD/TPI 35 mg/m² twice daily on days 1–5 and days 8–12 of each 28-day treatment cycle until the disease progressed or the patient developed intolerance to the treatment.

Evaluation and statistical analysis

The tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors, version 1.1. OS was defined as the period from date of initiation of treatment with FTD/TPI to death. Patients who were alive or whose data were missing at the cut-off point were censored. PFS was considered as the duration between the date of initiation of treatment with FTD/TPI and disease progression or death from any cause. Patients whose information regarding tumor progression was missing were censored. OS and PFS were estimated using the Kaplan–Meier method. Statistical analyses were performed using JMP software, version 12 (SAS Institute Inc., Cary, NC, USA). Toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 4.1.

Evaluation of ascites

We assessed the extent of ascites using computed tomographic scans, based on which the patients were categorized into the following groups: massive (extending throughout the abdominal cavity), moderate (neither mild nor massive), mild (localized at the pelvic cavity or liver surface), or no ascites (ascites not detected). Moderate or massive ascites were defined as high ascites burden (HAB) and mild or no ascites as low ascites burden (LAB) based on previous reports [6, 7].

Results

Between January 2019 and July 2021, 44 patients received FTD/TPI after failure of at least two prior regimens. Their characteristics are shown in Table 1. The median age was 71 (range, 37–85) years and a majority of the patients were men (70%). The numbers of patients with Eastern Cooperative Oncology Group performance status scores of 0, 1, and 2 were 8 (18%), 32 (73%), and 4 (9%), respectively. While 34 patients (77%) had peritoneal dissemination, 25 (57%) had ascites, of whom 13 (30%) were considered as having HAB. Most of the patients (97%) had received prior regimens containing 5-fluorouracil, platinum drug, taxane, and ramucirumab. While 41 patients (93%) had received nivolumab previously, 12 (27%) had undergone treatment with a regimen comprising CPT-11.

Table 1
Characteristics of study participants

Total number of participants	**44**
Sex (male)	31 (70%)
Age (years), median (range)	71 (37–85)
PS score	
0	8 (18%)
1	32 (73%)
2	4 (9%)
Histology (diffuse type)	25 (57%)
HER2 status (positive)	10 (23%)
Prior gastrectomy	17 (39%)
Metastases to more than one organ	34 (77%)
Liver metastasis	14 (42%)
Peritoneum dissemination	34 (77%)
Ascites	25 (57%)
High ascites burden	13 (30%)
Number of prior regimens	
2	3 (7%)
3	26 (59%)
> 3	15 (34%)
Prior regimens	
5-FU	43 (98%)
Platinum	41 (93%)
Taxane	42 (95%)
CPT-11	12 (27%)
Ramucirumab	41 (93%)
Nivolumab	41 (93%)
PS, performance status; HER2, human epidermal growth factor receptor 2; 5-FU, 5-fluorouracil	

Efficacy

A partial response was observed among 2% of the patients, and 41% showed stable disease, resulting in a response rate (RR) of 2% and a disease control rate (DCR) of 43%. The median follow-up time was 5.8 (range, 1.0–26.6) months for the censored patients. The median PFS was 2.4 months (95% confidence interval [CI], 1.9–3.5), and the median OS was 5.8 months (95% CI, 4.5–7.4; Fig. 1). The efficacy of treatment in patients with ascites (RR, 0%; DCR, 25%; median PFS, 2.2 months [95% CI, 1.7–2.8]; and OS, 4.7 months [95% CI, 3.7–6.1]) and that of those without ascites (RR, 8%; DCR, 68%; median PFS, 3.9 months [95% CI, 1.9–4.4]; and OS, 8.6 months [95% CI, 5.2–13.5]) are depicted in Figs. 2a and 2b. There were significant differences in OS (P = 0.0406) and DCR (P = 0.0012) between patients with and without ascites. Furthermore, the OS (4.3 vs. 7.2 months, P = 0.0033) was significantly worse in the HAB group than in the LAB group. The PFS (1.9 vs. 2.8 months, P = 0.2041; Figs. 2c, 2d), RR (0% vs. 3%, P = 0.5124) and DCR (23% vs. 48%, P = 0.1192) were poor in the HAB group compared with those in the LAB group, although the differences were not statistically significant (Table 2). Only one patient each among those with ascites (4%) and those with HAB (8%) demonstrated reduced ascites.

Table 2
Responses among patients with measurable lesions

	All (n = 44)	With Ascites (n = 25)	Without ascites (n = 19)	HAB (n = 13)	LAB (n = 31)
CR	0	0	0	0	0
PR	1	0	1	0	1
SD	17	5	12	3	14
PD	26	20	6	10	16
RR (%)	2%	0%	5%	0%	3%
		OR: NE (95% CI: NE)		OR:NE (95% CI: NE)	
		P = 0.2459		P = 0.5124	
DCR (%)	41%	20%	68%	23%	48%
		OR: 8.67 (95% CI: 2.19–34.43)		OR: 3.13 (95% CI: 0.72–13.59)	
		P = 0.0012		P = 0.1192	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate; DCR, disease control rate (CR + PR + SD); HAB, high ascites burden; LAB, low ascites burden; OR, odds ratio; NE, not evaluated; CI, confidence interval

Safety

Adverse events that occurred among the study participants are shown in Table 3; the major ones were neutropenia (45%), anemia (30%), infection (11%), decreased platelet count (7%), fatigue (7%), and anorexia (6%). There was no significant difference in the frequency of occurrence of adverse events of grade 3 or higher (P = 0.6804) between patients with and without ascites. Similarly, no significant difference was observed in this frequency between the HAB and LAB groups (p = 0.16).

Table 3
Frequency of occurrence of adverse events among study participants

	All (n = 44)		**With ascites (n = 25)**		**Without ascites (n = 19)**	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Fatigue	21 (48%)	3 (7%)	11 (44%)	2 (8%)	10 (53%)	1 (5%)
Anorexia	23 (52%)	2 (5%)	15 (60%)	2 (8%)	8 (42%)	
Nausea	13 (30%)		9 (36%)		4 (21%)	
Vomiting	6 (14%)		4 (16%)		2 (11%)	
Diarrhea	4 (9%)		2 (8%)		2 (11%)	
Infection	7 (16%)	5 (11%)	3 (12%)	2 (8%)	4 (21%)	3 (16%)
Dysgeusia	1 (2%)				1 (5%)	
Mucositis	1 (2%)		1 (4%)			
Brain infarction	1 (2%)	1 (2%)	1 (4%)	1 (4%)		
Febrile neutropenia	1 (2%)	1 (2%)	1 (4%)	1 (4%)		
Neutropenia	23 (52%)	20 (45%)	9 (36%)	7 (28%)	14 (74%)	13 (68%)
Anemia	29 (66%)	13 (30%)	16 (64%)	6 (24%)	13 (68%)	7 (37%)
Decreased platelet count	8 (18%)	3 (7%)	4 (16%)	1 (4%)	4 (21%)	2 (11%)

Dose modification was warranted in 64% of the patients (dose reduction, 30%; dosing delay, 59%). There was no significant difference in the frequency of dose reduction between the patients with and without ascites (32% vs. 26%, p = 0.6813) as well as between the HAB and LAB groups (23% vs. 32%, p = 0.5366).

Treatment was terminated because of progressive disease in 43 patients, among whom 17 (28%) received subsequent therapy. Of them, 7 patients (16%) received CPT-11-based regimen; 3 (8%),

nivolumab; 3 (8%), trastuzumab deruxtecan; 2 (5%) capecitabine plus trastuzumab, 1 (2%) capecitabine plus oxaliplatin plus trastuzumab; and 1 (2%), S-1 plus oxaliplatin with paclitaxel. There was no significant difference in treatment-transition rate between patients with and without ascites (28% vs. 39%, P = 0.4535), although it was significantly lower in the HAB group than in the LAB group (8% vs. 43%, P = 00131).

Discussion

In this retrospective study, we used real-world data regarding treatment of patients with AGC using FTD/TPI. We observed levels of efficacy and safety that were similar to those demonstrated in the TAGS trial, namely an RR of 4%, PFS of 2 months, OS of 5.7 months among patients undergoing third- or higher-line chemotherapy. However, there are some differences between the results of our study and those of the TAGS trial. In the TAGS trial, 63% of the patients received three or more number of prior regimens, and 34% received ramucirumab. In our study, 91% of the patients received three or more number of prior regimens, and 93% received ramucirumab. Our study included higher numbers of older patients, patients with poorer PS, and patients who underwent more pretreatments; all these factors reflected the situation in clinical practice. Our study suggests that FTD/TPI is an important regimen for treatment of patients with AGC who have received ramucirumab.

Immune check point inhibitors (ICIs), such as nivolumab, are one of the most important drugs used to treat AGC. The ATTRACTION-2 trial showed a significant clinical benefit in patients with AGC who had previously received two or more prior chemotherapy regimens [8]. In addition, nivolumab plus chemotherapy significantly improved OS compared with the use of chemotherapy alone in the CHECKMATE649 trial and has become the standard first-line treatment [2]. Although FTD/TPI in the third- or later- line chemotherapy is more effective when nivolumab is used in the first-line treatment, the efficacy and safety of FTD/TPI after administration of ICIs were unclear. In the TAGS trial, only 7% of the patients received ICIs before administration of FTD/TP, while in our study, 94% of the patients received ICIs before FTD/TPI administration, and the efficacy and safety exhibited in our study were similar to those in the TAGS trial, which suggests that FTD/TPI is one of the key drugs for treatment of AGC after administration of ICIs.

In our study, 48% of the patients experienced adverse events of grade 3 or 4. Furthermore, compared with the TAGS trial, our study had a similar safety profile and more cases requiring dose reduction or postponement.

Considering the results of the phase 3 trial of FTD/TPI in patients with colorectal cancer (CRC)[9, 10], it is possible that there are many cases of dose reduction and dosing delay when FTD/TPI is used to treat AGC. Although, the patient background is different, the frequency with which non-hematological toxicity of FTD/TPI occurs is higher in patients with AGC than in those with CRC [9, 10]. Thus, compared with patients having CRC, those with AGC treated using FTD/TPI require careful management. It has been

suggested that biweekly administration of FTD/TPI may reduce toxicity in patients with CRC compared with normal dosages of FTD/TPI [11]; a similar investigation related to AGC is awaited.

Peritoneal dissemination is common in patients with AGC, approximately 40% of whom exhibit ascites as a clinical symptom [12, 13]. We found that there were significant differences in OS and DCR between patients with and without ascites. In addition, OS was significantly shorter in patients with HAB. There was no significant difference in the frequency of occurrence of adverse events of grade 3 or higher between patients with and without ascites. Therefore, FTD/TPI may be well tolerated, although the effect is inadequate in patients with AGC having ascites.

Kawazoe et al. [14] reported that in patients with AGC previously treated with second- to fourth- lines chemotherapy, FTD/TPI plus ramucirumab showed promising efficacy (RR, 16%; DCR, 77%; PFS, 5.3 months). Increased vascular endothelial growth factor receptor 2 ligand in patients with ascites may be associated with poor prognosis, and FTD/TPI plus ramucirumab may be effective in treating patients with AGC having ascites [15]. Nevertheless, data related to the efficacy and safety of this treatment is not available.

This study had certain limitations. It was a retrospective analysis, and the sample size was small. Therefore, a prospective multicenter study involving more patients with AGC having ascites must be conducted to clarify the efficacy and safety of FTD/TPI in this population.

Conclusions

In conclusion, our results indicate that FTD/TPI had modest efficacy and tolerable toxicity in patients with AGC patients having ascites. However, considering the effectiveness of this treatment is inadequate, further research focusing on improving efficacy is needed.

Declarations

Ethics approval and consent to participate

All procedures were performed in accordance with institutional and national standards on human experimentation as confirmed by the ethics committee of all institutions and with the Helsinki Declaration of 1964 and its later amendments. This study was approved by the Institutional Review Board of the Kobe City Medical Center General Hospital (examination number: zn211018), Himeji Red Cross Hospital, and Osaka Red Cross Hospital. The requirement for informed consent was waived because this was an observational study. However, we followed the opt-out consent approach, which was approved by the ethics committee of the Kobe City Medical Center General Hospital and Himeji Red Cross Hospital. All administrative permissions to access the data used in this research were acquired.

Consent for publication

Not applicable

Availability of data and materials

All the data and materials supporting the conclusions are included in the main paper. The datasets used in the current study are available from the corresponding author on reasonable request.

Conflicts of interest

Hironaga Satake received research funding from Ono Pharmaceutical Co., Ltd.; Daiichi Sankyo Co., Ltd.; Taiho Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Co., Ltd.; and Sanofi Co., Ltd. as well as honoraria from Bayer Co., Ltd.; Bristol-Myers Squibb Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; Daiichi Sankyo Co., Ltd.; Eli Lilly Japan Co., Ltd.; Merck Bio Pharma Co., Ltd.; MSD Co., Ltd.; Ono Pharmaceutical Co., Ltd.; Sanofi Co., Ltd.; Taiho Pharmaceutical Co., Ltd.; Takeda Co., Ltd.; and Yakult Honsha Co., Ltd.

All the remaining authors declare that they have no competing interests.

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Authors' contributions

TM, SY, YK, HN, TK, TT, YM, MT, HY, and H-S participated in literature search, data acquisition, data analysis, and data interpretation. TM conceived and designed the study, critically revised the manuscript, performed the research, wrote the first draft, and collected and analyzed the data. TM, SY, YK, HN, TK, TT, YM, MT, HY, and HS wrote and revised the manuscript. All authors have read and approved the manuscript.

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Figures

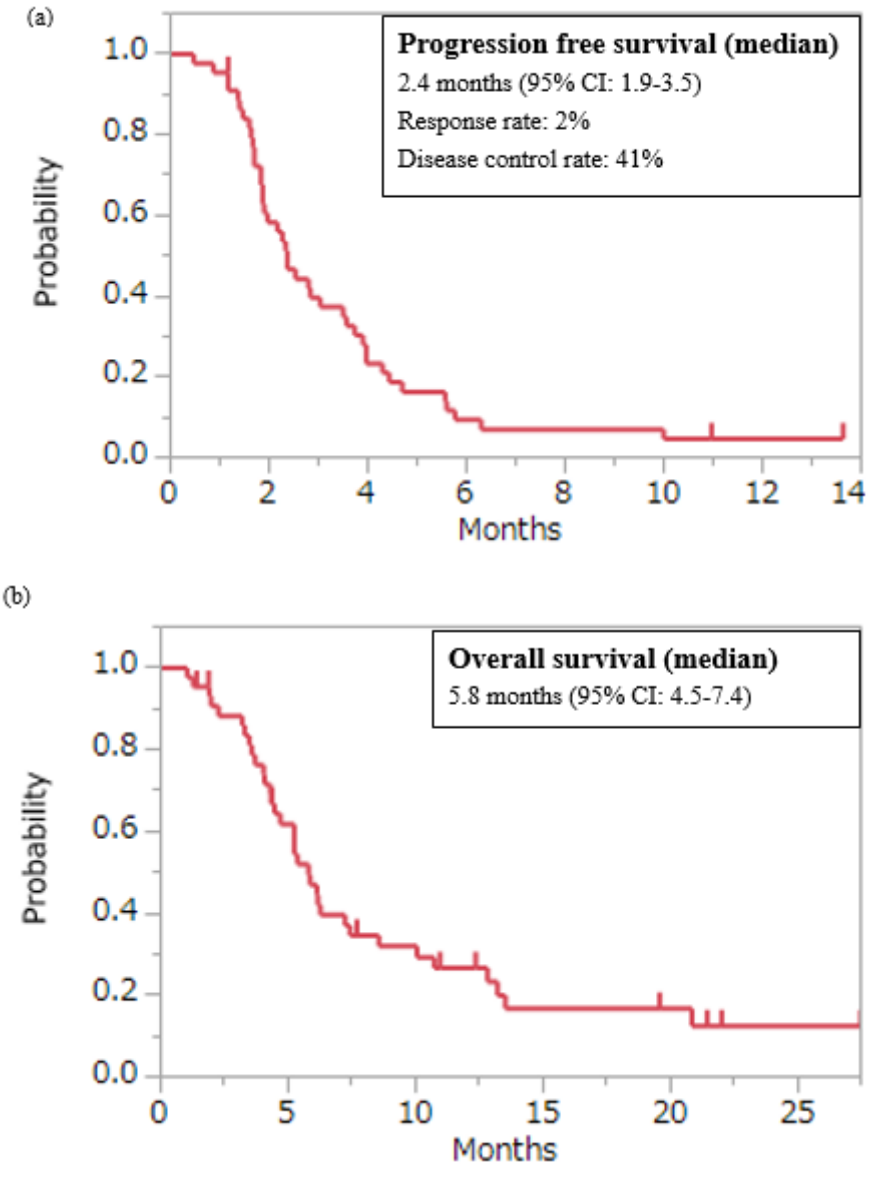

Figure 1

Kaplan–Meier plots of (a) progression-free survival and (b) overall survival among study participants

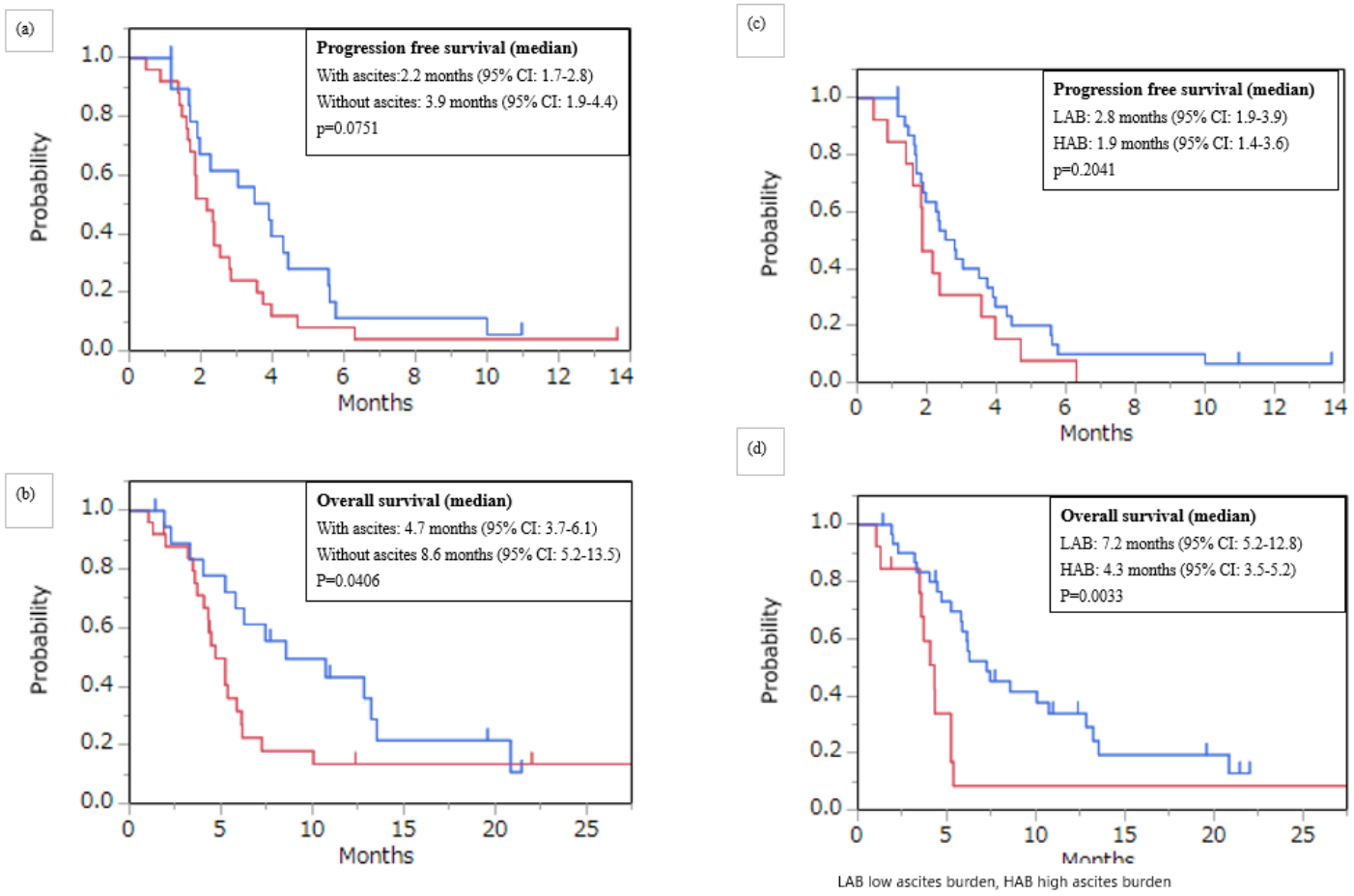

Figure 2

Kaplan–Meier plots of (a) progression-free survival and (b) overall survival among study participants (red line indicates patient group with ascites; blue line indicates patient group without ascites).

Kaplan–Meier plots of (c) progression-free survival and (d) overall survival among study participants (red line indicates patient group with HAB; blue line indicates patient group with LAB).

HAB, high ascites burden; LAB, low ascites burden