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Effect of Diabetes on Outcomes in Patients With Incurable/Unresectable and Advanced/Recurrent Colorectal Cancer Receiving mFOLFOX6

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Abstract. *Background/Aim: The high mortality rate associated with colon cancer in patients with diabetes is well-established; however, the underlying mechanisms have not been fully elucidated. Here, we investigated the efficacy of modified FOLFOX6 (mFOLFOX6) therapy, which is frequently used in colon cancer treatment, in patients with and without comorbid diabetes. Patients and Methods: The participants in this retrospective cohort study received mFOLFOX6 therapy as a first-line treatment for incurable/unresectable and advanced/recurrent colon cancer. We compared patient background characteristics; number of mFOLFOX6 courses; total dose of each drug; reasons for dose reduction, deferment, or discontinuation; and survival time. Results: Data of six patients with diabetes and 26 without diabetes were assessed. There was no significant difference in background characteristics between the patient groups, with the exception of blood glucose levels. There was no significant difference in the planned number of mFOLFOX6 courses between the groups; however, the total number of completed courses was significantly lower in patients with diabetes than in those without diabetes. Discontinuation rates due to adverse events were similar between the groups; however, discontinuation due to progressive disease or death was significantly higher in patients with diabetes than in those without diabetes. No significant differences were observed in the total dose of each anticancer drug or survival time between the groups. Conclusion: mFOLFOX6 may not have sufficient therapeutic effects in patients with diabetes. Therefore, in patients with concurrent diabetes and colon cancer, alternative therapeutic options for cancer treatment should be considered.*

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Patients with diabetes reportedly have a higher risk of developing various cancers, including colon cancer, with higher mortality rates than those without diabetes (1-4). The mechanisms underlying this relationship remain poorly understood, although hyperglycemia, hyperinsulinemia, and chronic inflammation have been suggested to play a role (4, 5). Our previous preclinical study showed that cancer metastasis is more likely to occur in mice models of hyperglycemia (6).

Chemotherapy is one of the main approaches for cancer treatment. Patients with diabetes reportedly have a high frequency of adverse events (such as oxaliplatin-induced peripheral neuropathy, fluorouracil-induced diarrhea, and peripherally inserted central catheter-associated infections) during cancer chemotherapy as well as shorter overall and disease-free survival times (7-11) than those without diabetes. These findings suggest that individuals with diabetes might

experience suboptimal therapeutic outcomes from anticancer medications, either due to adverse effect-related treatment interruptions or the inherent ineffectiveness of these drugs. Currently, there is no established treatment method that is both highly effective and safe for patients with diabetes.

The main treatment approaches for colon cancer are surgery and chemotherapy. Adjuvant chemotherapy aims to suppress postoperative recurrence, and drug therapy for incurable/unresectable and advanced/recurrent colon cancer aims to prolong life and alleviate symptoms. For cases of incurable/unresectable and advanced/recurrent colon cancer, chemotherapy plays an important role in improving prognosis. In Japan, modified FOLFOX6 (mFOLFOX6), which contains oxaliplatin and fluorouracil, is a first-line treatment for incurable/unresectable and advanced/recurrent colon cancer (12). In our previous study, we observed the effects of oxaliplatin/fluorouracil administration in a mice model of hyperglycemia in which cancer cells were transplanted. The study revealed that the survival time of hyperglycemic mice was shorter than that of mice with normal blood glucose levels, and that oxaliplatin/fluorouracil administration did not prolong survival in the hyperglycemic group (13). However, it is unclear whether this result is applicable to clinical practice.

In this study, we sought to clarify the efficacy and safety of mFOLFOX6 in patients with diabetes by investigating those with incurable/unresectable and advanced/recurrent colon cancer who received mFOLFOX6-containing cancer chemotherapy as a first-line treatment.

Patients and Methods

Study design and patients. We performed a retrospective cohort study and compared the outcomes of patients with and those without diabetes. We extracted the data of patients who received mFOLFOX6 chemotherapy with or without molecularly targeted drugs as a first-line treatment for incurable/unresectable advanced or recurrent colorectal cancer between July 2011 and June 2014 at Kobe City Medical Center General Hospital, Japan. The regimen of conventional mFOLFOX6 includes a 2-h infusion of 85 mg/m^2 oxaliplatin and 200 mg/m^2 l-leucovorin, and a 5-min bolus infusion of 400 mg/m^2 fluorouracil, followed by a 46-h continuous infusion of 2,400 mg/m^2 fluorouracil. It is repeated every 14 days until progressive disease occurs. A 5-hydroxytryptamine-3 receptor inhibitor and dexamethasone were given as antiemetics. The exclusion criteria were as follows: patients aged <20 years, non-Japanese patients, patients lost to follow-up despite receiving treatment, patients on no medications for diabetes despite glucose levels >160 mg/dl on random blood glucose testing, or patients who developed diabetes after mFOLFOX6 treatment initiation. Patients diagnosed with diabetes and receiving one or more anti-diabetic agents [insulin, sulfonylurea, glinide, dipeptidyl peptidase 4 (DPP4) inhibitor, glucagon-like peptide-1 antagonist, biguanide, α-glucosidase inhibitor, thiazolidine, or sodium-glucose transporter 2 inhibitors] were enrolled as patients with diabetes, and all others were enrolled as patients without diabetes. Follow-up was conducted until December 2020.

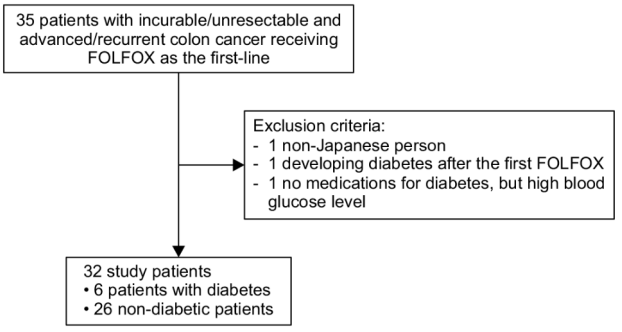

Figure 1. *Study flowchart*.

Outcome measures. The following items were evaluated retrospectively using the electronic health record system: patients' baseline characteristics (sex, age, height, weight, and stage of cancer at mFOLFOX6 initiation), diabetic condition (type of diabetes, glucose level, and use of anti-diabetic medication), regimen (classes of combined molecularly targeted drugs or not), duration of mFOLFOX6 chemotherapy (total courses and those received according to the regimen), total dose of oxaliplatin and fluorouracil (bolus and continuous infusion), adverse events that led to dosage reduction, deferment, or discontinuation of mFOLFOX6, reasons for the discontinuation of mFOLFOX6, and overall survival.

Statistical analysis. Differences between patients with and those without diabetes were evaluated using Fisher's exact test, student's *t*-test, Welch test, or Mann–Whitney *U*-test as appropriate. Duration of mFOLFOX6 chemotherapy and overall survival were estimated using Kaplan–Meier analysis with a log-rank test. The hazard ratio (HR) for overall survival and 95% confidence interval (CI) were estimated using a Cox proportional hazards regression model. All statistical analyses were performed using SPSS Statistics 29.0.0 (IBM Japan, Tokyo, Japan). Differences were considered significant at $p<0.05$.

Ethical considerations. This study was conducted in accordance with the tenets of the Declaration of Helsinki. Opt-out approach was employed for the use of participant data for research purposes. This study protocol and consent procedure were reviewed and approved by the Ethics Committees of Kobe City Medical Center General Hospital (approval number: zn160405, date of approval: May 24, 2016) and by the Ethics Committees of Kobe Gakuin University (approval number: HEB17-07, date of approval: July 26, 2017).

Results

Patient background. Figure 1 shows the study flowchart. During the study period, 35 patients with incurable/unresectable and advanced/recurrent colon cancer received mFOLFOX6 as a first-line treatment. Of these, one non-Japanese patient, one patient who was diagnosed with diabetes after starting mFOLFOX6, and one patient who was not receiving anti-diabetic drugs but had a blood glucose level of >160 mg/dl were excluded. Therefore, data from 32 patients were analyzed.

Table I. *Baseline characteristics of the patients.*

	Non-DM (n=26)	DM (n=6)	*p*-Value
Sex male, n (%)/female, n (%)	13 (50.0%)/13 (50.0%)	4 (66.7%)/2 (33.3%)	0.659[a]
Age (years)*	64.0±9.5	68.7±10.7	0.300[b]
Body weight (kg)*	53.5±12.4	63.8±14.2	0.087[b]
Body mass index (kg/m^2)*	20.3±3.3	23.3±2.6	0.050[b]
Body surface area (m^2)*	1.55±0.21	1.70±0.24	0.141[b]
StageI/II/III/IV[#]	0/1/8/16	0/0/3/3	
Glucose (mg/dl)*	103.5±15.7	151.3±37.8	0.026[c]
Anti-diabetic agents, n (%)			
SU/Glinide	-	4 (66.7%)	
DPP4 inhibitor	-	3 (50.0%)	
Biguanide	-	3 (50.0%)	
α-Glucosidase inhibitor	-	2 (33.3%)	
Thiazolidine	-	1 (16.7%)	
Insulin	-	1 (16.7%)	

*Mean±SD; [#]n=25 (non-DM), 6 (DM). [a]Fisher's exact test; [b]Student *t*-test; [c]Welch test.

Table I shows the patient background characteristics. Of the target patients, six had diabetes and 26 did not. There were four male patients with diabetes (66.7%) and 13 without diabetes (50.0%) (p=0.659). The mean age was 68.7±10.7 years for patients with diabetes and 64.0±9.5 years for patients without diabetes (p=0.300). The mean blood glucose level was 151.3±37.8 mg/dl in patients with diabetes and 103.5±15.7 mg/dl in those without diabetes (p=0.026). With the exception of the blood glucose level, there was no notable difference in patient background characteristics between the diabetic and non-diabetic groups. Among the patients with diabetes, the most commonly used anti-diabetic agents were insulin secretagogues such as sulfonylureas and glinide (n=4, 66.7%), followed by DPP4 inhibitors and biguanide (n=3 each, 50.0%).

Regimen used. We investigated molecularly targeted drugs used in combination with mFOLFOX6 at the start of mFOLFOX6 therapy. The breakdown of the combinations used for the following drugs between patients with diabetes and those without diabetes were as follows: bevacizumab, three (50.0%) *vs*. 16 (61.5%) patients; cetuximab, zero *vs*. four (15.4%) patients; and panitumumab, one (16.7%) *vs*. one (3.8%) patients (p=0.459).

Number of administered treatment courses. Figure 2 shows the number of completed mFOLFOX6 courses (no drug reduction, deferment, or discontinuation) and the total implemented number of courses, including drug reduction and deferment. The median (range) number of courses where treatment was completed according to the regimen was 1.0 (0-10) for patients with diabetes and 3.0 (0-15) for those without diabetes (p=0.204; Figure 2A). The median (range) of the total implemented number of courses was 10.5 (1-17) for patients with diabetes and 16.0 (1-50) for those without diabetes (p=0.035; Figure 2B).

Total oxaliplatin/fluorouracil dose. Figure 3 shows the total dose of anticancer drugs administered during the mFOLFOX6 treatment period. The median (range) total dose of oxaliplatin was 513 (83-1,409) mg/m^2 for patients with diabetes and 659 (75-1,595) mg/m^2 for patients without diabetes (p=0.494; Figure 3A). The median (range) total dose of bolus fluorouracil was 2,650 (388-5,966) mg/m^2 in patients with diabetes and 4,573 (324-19,655) mg/m^2 in patients without diabetes (p=0.207; Figure 3B). The median (range) total dose of continuous fluorouracil infusion was 24,141 (2,354-40,566) mg/m^2 in patients with diabetes and 35,638 (2,082-117,928) mg/m^2 in patients without diabetes (p=0.131; Figure 3C).

History of mFOLFOX6 reduction, deferment, or discontinuation. We investigated the main adverse effects that led to reduction, deferment, or discontinuation of mFOLFOX6 therapy from treatment initiation to the 12th course. During the first 12 courses, six patients with diabetes (100.0%) and 22 patients without diabetes (84.6%) either reduced, deferred, or discontinued mFOLFOX6. Cytopenia was the cause of dose reduction, deferment, or discontinuation in one patient with diabetes (16.7%) and 12 patients without diabetes (46.2%) (p=0.361). Peripheral neuropathy was the cause in one patient with diabetes (16.7%) and 10 patients without diabetes (38.5%) (p=0.637). One patient with diabetes (16.7%) and four patients without diabetes (15.4%) (p=1.000) reduced, deferred, or discontinued therapy due to an infection. There were no differences in the main adverse

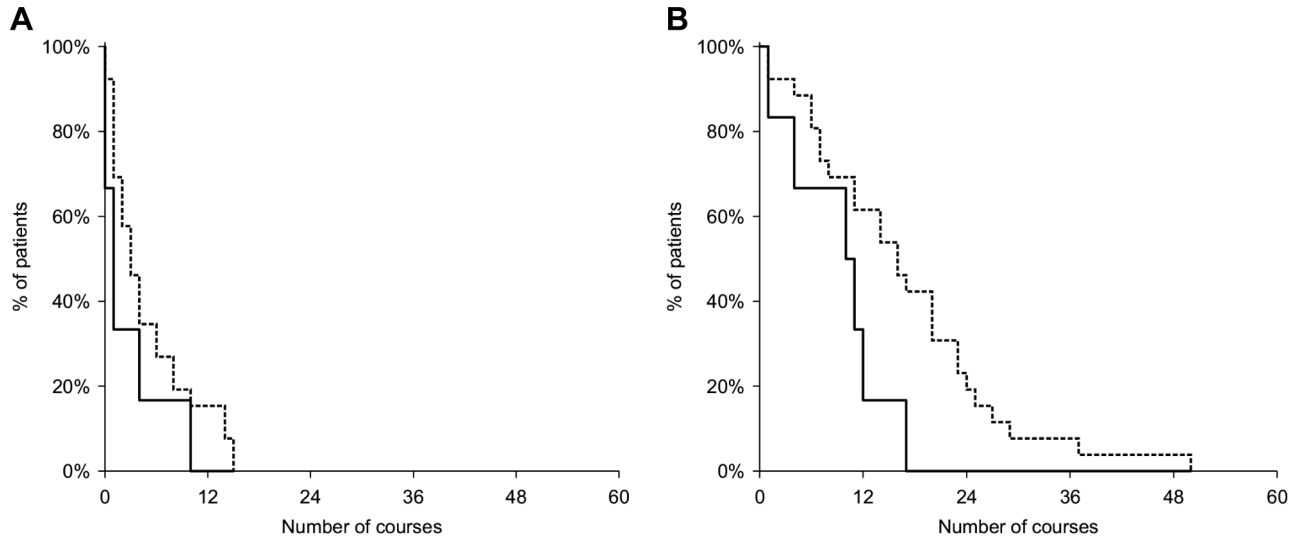

Figure 2. *Number of completed mFOLFOX6 courses in patients with and without diabetes. (A) Implemented number of courses according to regimen (no reduction or deferment), (B) total implemented number of courses: horizontal axis represents the implemented number of courses and vertical axis represents the number of patients who completed the number of courses on the horizontal axis; (A) p=0.204; (B) p=0.035 (log-rank test); dashed line: non-diabetic patients; solid line: patients with diabetes.*

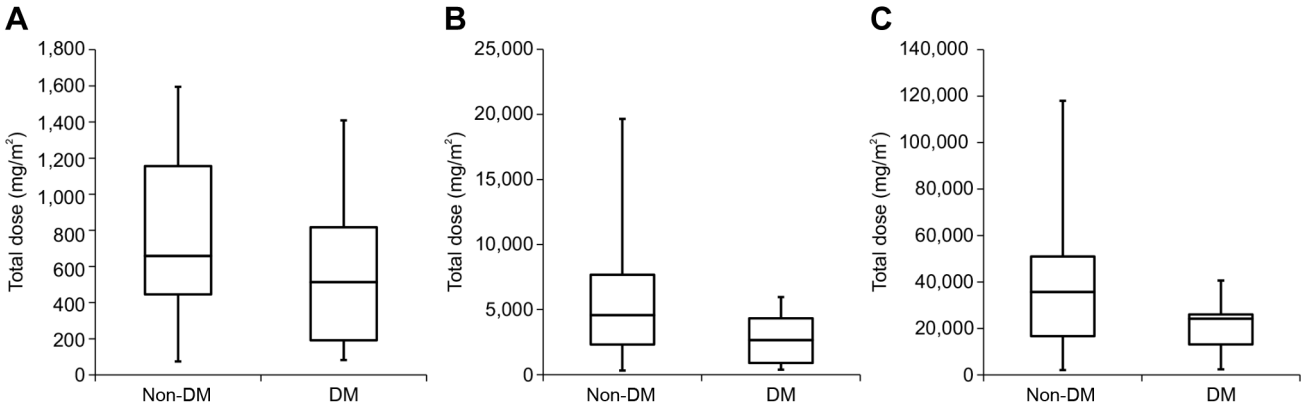

Figure 3. *Total dose of each drug during the mFOLFOX6 administration period in patients with and without diabetes. (A) oxaliplatin, (B) fluorouracil (bolus), and (C) fluorouracil (continuous infusion). The line in the center of the box indicates the median, and the upper and lower lines are the 75th and 25th percentiles, respectively. (A) p=0.494, (B) p=0.207, (C) p=0.131 (Mann–Whitney U-test).*

effects leading to mFOLFOX6 reduction, deferment, or discontinuation between patients with and those without diabetes.

mFOLFOX6 therapy discontinuation during the first 12 courses was due to adverse effects in one patient with diabetes (16.7%) and four patients without diabetes (15.4%) (p=1.000), and due to progressive disease or death in three patients with diabetes (50.0%) and two patients without diabetes (7.7%). Significantly more patients with diabetes discontinued therapy due to progressive disease or death (p=0.034) (Table II).

Survival time after the initiation of mFOLFOX6 therapy. Figure 4 shows the survival time of patients with and those without diabetes after starting mFOLFOX6 treatment. During the study period, all six patients with diabetes died. Although four of the 26 patients without diabetes completed the treatment, their subsequent progress was unknown. There was no significant difference in survival between the groups (p=0.189) [hazard ratio (HR)= 0.546; 95% confidence interval (CI)=0.216-1.381]. Two patients with diabetes died of cancer. In four patients, including one patient who died within one month of starting mFOLFOX6 treatment, the

Table II. *Reasons for the discontinuation of mFOLFOX6 therapy.*

	Non-DM (n=26)	DM (n=6)	*p*-Value
Progression/death	2 (7.7%)	3 (50.0%)	0.034[a]
Adverse events	4 (15.4%)	1 (16.7%)	1.000[a]

[a]Fisher's exact test.

cause of death was unknown or not recorded. Treatment was switched to a different regimen after discontinuing mFOLFOX6 in four out of six patients with diabetes (66.7%) and in 17 out of 26 patients without diabetes (65.4%).

Discussion

In this study, we examined whether decreased treatment efficacy contributes to the elevated mortality rate in patients with comorbid colon cancer and diabetes. We specifically focused on mFOLFOX6 therapy, a commonly utilized treatment for colon cancer in clinical settings. We included patients with colon cancer who received mFOLFOX6 as a first-line therapy and compared the number of treatment courses, reason(s) for treatment discontinuation, and survival time between patients with and without diabetes. The results showed that patients with diabetes had an insignificantly lower number of planned mFOLFOX6 courses and total dose of anticancer drugs, significantly lower number of completed courses, and significantly higher rate of discontinuation due to progressive disease or death than patients without diabetes. However, the survival time did not significantly differ between the patient groups. Similarly, no differences were found in patient background characteristics, particularly in cancer stage and applied regimen (additional molecularly targeted drugs; Table I); hence, these factors are unlikely to have affected the results.

In patients with diabetes, there was a tendency to have a lower implemented number of mFOLFOX6 courses according to the regimen, although this difference was not significant (Figure 2A). However, patients with diabetes had a significantly lower total number of completed mFOLFOX6 courses (Figure 2B). Furthermore, the rates of discontinuation due to adverse effects did not significantly differ between the groups; however, discontinuation due to progressive disease or death was more common in patients with diabetes (Table II).

Peripheral neuropathy is a common complication of diabetes, and reports have indicated that patients with diabetes have a high incidence of peripheral neuropathy following oxaliplatin treatment (7-9). While the increased rates of mFOLFOX6 treatment reduction, deferment, and discontinuation in patients with diabetes may have been due to peripheral neuropathy, in practice, no differences were observed between the patient groups. During FOLFOX therapy, the cumulative dose (median)

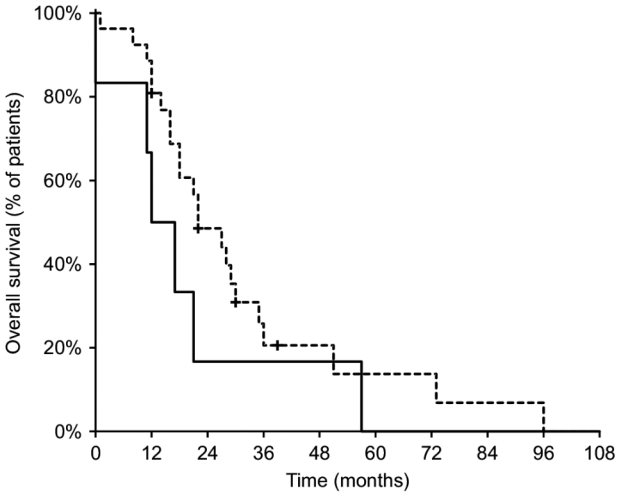

Figure 4. *Overall survival after the initiation of mFOLFOX6 therapy in patients with and without diabetes. Dashed line: patients without diabetes; solid line: patients with diabetes. Whiskers indicate censoring. p=0.189 (log-rank test).*

of oxaliplatin that causes grade 2 or 3 peripheral neuropathy is approximately 850 mg/m^2 (10th cycle) (14, 15). The results of our study may have derived because patients with diabetes discontinued mFOLFOX6 due to progressive disease or death prior to the worsening of peripheral neuropathy. In the present study, we were unable to determine whether peripheral neuropathy was more likely to occur depending on the presence or absence of diabetes.

The survival time did not differ between patients with and those without diabetes. This is because many patients switched to other cancer chemotherapies after first-line therapy with mFOLFOX6, and the results suggested that these alternative regimens were efficacious (*i.e.*, contributing to prolonged survival time).

Several differences exist between our real-world clinical results of administering mFOLFOX6 to patients with incurable/unresectable and advanced/recurrent colon cancer based on the presence or absence of diabetes and previously reported results in mouse models that were administered oxaliplatin/fluorouracil (13). Regarding efficacy, early treatment discontinuation due to cancer progression or death was common in patients with diabetes. There was almost no

tumor growth-suppression effect of oxaliplatin/fluorouracil therapy in a mouse model of hyperglycemia. These findings suggest that mFOLFOX6 has lower efficacy in patients with comorbid diabetes, in both clinical practice and animal models. Although survival time did not differ between the groups in the present study, it was shorter in mouse models of hyperglycemia. In animal experiments, a fixed amount of a given drug was administered, and no changes in treatment methods were made. However, in practice, treatment was reduced, deferred, or discontinued due to adverse effects, physical condition, and patient decision. Additionally, therapeutic effects following second-line treatment add complexity, making a thorough examination of the effect of mFOLFOX6 on survival challenging in patient-based clinical studies. Furthermore, the blood glucose levels were controlled with drugs in patients with diabetes, which was not done in animal models of hyperglycemia. Patients with poor blood glucose control are more likely to develop fluorouracil-related toxicity (16). The above results suggest that mFOLFOX6 may not be effective in prolonging survival in patients with diabetes, at least in those with blood glucose levels not well-controlled.

Georgescu *et al*. (17) suggested that the presence of diabetes at diagnosis of locally advanced rectal cancer may be a negative predictive factor for response to neoadjuvant therapy, distant metastases, and local recurrences rates. Our results are broadly consistent with those of Georgescu *et al*., but there were differences in the therapeutic approach. Abdel-Rahman (18) compared the efficacy and safety of mFOLFOX6 for metastatic colon cancer in patients with and without diabetes. In that study, no differences in overall survival were observed between the patient groups, and the time of onset of paresthesia was shorter in patients with diabetes; however, the incidence or severity of paresthesia did not differ between groups. These results are also consistent with our present findings. In contrast to this previous study, which revealed no difference in progression-free survival, our study showed that treatment discontinuation due to cancer progression or death occurred more frequently in patients with diabetes. This discrepancy in the findings can be attributed to the challenges in making a generalized comparison, arising from variations between phase III trials and real-world clinical practice, differences in target patients (e.g., race, stage, and concomitant medications), and evaluation methods.

Study limitations. First, the number of patients was small. Specifically, we only included six patients with diabetes. We focused on patients within a single hospital over three years. However, as the study specifically concentrated on individuals with incurable/unresectable and advanced/recurrent colon cancer, the targeted number of patients may be insufficient. Second, this was a retrospective study, and there were a few evaluations based on objective indicators. Moreover, this was not an interventional study; instead, we examined patients who had already concluded their treatment. Third, we were unable to observe the effects of concomitant medications, including molecularly targeted drugs and anti-diabetic agents. Reports have indicated that insulin and sulfonylureas may promote cancer progression (5, 19, 20) and that metformin reduces the risk of cancer onset and death (5, 21, 22). However, in the present study, the number of patients with diabetes was small; hence, we could not compare the effects of such combinations.

Conclusion

In this retrospective cohort study, we found that more patients with diabetes discontinued mFOLFOX6 treatment because of cancer progression or death, and completed significantly fewer courses of mFOLFOX6 therapy than patients without diabetes. However, no significant differences in survival time were observed, and many patients who discontinued mFOLFOX6 switched to other therapies. Therefore, even if treatment with mFOLFOX6 failed in patients with diabetes, cancer treatment may be successful with alternative regimens. Our study results suggest that mFOLFOX6 may not have sufficient therapeutic efficacy in patients with diabetes. Despite the limited number of patients, our study provides valuable insights for decision-making regarding cancer chemotherapy strategies in patients with diabetes.

Conflicts of Interest

Hisateru Yasui received honoraria from Yakult Honsha.

Authors' Contributions

Mai Ikemura: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Project administration; Visualization; Writing – original draft. Masaki Hirabatake: Data curation; Investigation; Supervision; Writing – original draft; Writing – review & editing. Megumi Aburaya: Data curation; Investigation; Writing – review & editing. Hiroaki Ikesue, Hisateru Yasui, Nobuyuki Muroi, Tohru Hashida: Supervision; Writing – review & editing.

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