Incidence of and risk factors for severe neutropenia during treatment with the modified FOLFIRINOX therapy in patients with advanced pancreatic cancer

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Research Article

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Abstract

Background

Although FOLFIRINOX (oxaliplatin, irinotecan, 5-FU, and *l*-leucovorin) is established as one of the standard therapies for patients with metastatic pancreatic cancer, the modified FOLFIRINOX (mFOLFIRINOX) is often used in clinical practice to reduce the incidence of toxicities. Febrile neutropenia (FN) and severe neutropenia during FOLFIRINOX are especially frequently observed in Japanese patients. In this study, we evaluated the incidence of FN and severe neutropenia, and explored the risk factors for severe neutropenia in patients receiving treatment with mFOFIRINOX.

Methods

The data of patients who had received mFOLFIRINOX between December 2013 and December 2014 at the National Cancer Center Hospital East were reviewed retrospectively. We graded the neutropenia severity and defined ≥ Grade 3 neutropenia as severe neutropenia. Univariate and multivariate analysis were undertaken to evaluate the associations with risk of development of severe neutropenia.

Results

A total of 122 patients were enrolled in this study. Sixty two patients (51%) and 10 patients (8%) developed severe neutropenia and FN, respectively. Multivariate analysis identified a low baseline white blood cell count (odds ratio [OR], 14.50; 95% confidence interval (CI), 3.27-111.14; $p = 0.002$) and presence of heterozygosity for *UGT1A1**28 or *UGT1A1**6 polymorphism (OR, 2.84; 95% CI, 1.18–7.17; $p = 0.023$) as independent risk factors for severe neutropenia.

Conclusion

The incidences of severe neutropenia and FN in patients receiving mFOLFIRINOX in our clinical practice were comparable to previous reports. The risk factors for severe neutropenia in patients receiving mFOLFIRINOX were a low baseline white blood cell count and presence of heterozygosity for *UGT1A1**28 or *UGT1A1**6 polymorphism.

Introduction

Pancreatic cancer is an aggressive malignant disease, with reported 5-year survival rates of less than 10% [1]. The American Cancer Society estimates that 55,440 patients were diagnosed as having pancreatic cancer and 44,330 deaths were caused by pancreatic cancer in 2018 [1]. In Japan, pancreatic cancer is the fourth leading cause of cancer-related death and the number of patients who died of the disease was 36,356 in 2019 [2].

For the treatment of metastatic pancreatic cancer (MPC), treatment with gemcitabine (GEM) alone, which was associated with a response rate of approximately 10% and yielded a median survival period of 5.65 months, was considered as the gold standard for more than 10 years [3, 4]. Then, in the ACCORD11 trial, a phase II / III study performed in 2011, FOLFIRINOX (oxaliplatin, irinotecan, 5-FU, and *l*-leucovorin) was demonstrated to significantly improve the overall survival (OS), progression-free survival (PFS), and quality of life as compared to GEM alone in patients with MPC [5]. In Japan, a phase II study conducted in 2014 demonstrated the efficacy of FOLFIRINOX as first-line treatment for MPC, and the treatment was approved in that setting [6]. Thereafter, a phase III study (MPACT) demonstrated better efficacy of GEM administered in combination with nab-paclitaxel (GEM + nab-PTX) as compared to GEM monotherapy in chemonaive MPC patients [7]. It is difficult to compare the efficacy of GEM + nab-PTX with that of FOLFIRINOX, because the patient characteristics of the enrolled patients in the studies were slightly different. Therefore, these two regimens are currently considered as the standard first-line treatments for MPC in Japan. The main adverse effects of FOLFIRINOX are hematological toxicities, gastrointestinal symptoms, including nausea, vomiting, and diarrhea, and peripheral neuropathy. In particular, febrile neutropenia (FN) and grade 3/4 neutropenia were observed more frequently in a Japanese phase II study of FOLFIRINOX (22.2% and 77.8%) as compared to the ACCORD11 trial (5.4% and 45.7%) [5][6]. Therefore, a modified regimen of FOLFIRINOX (mFOLFIRINOX), in which the irinotecan dose is reduced to 150 mg/m^2 and bolus 5-fluorouracil is omitted, is often administered in clinical practice to reduce the incidence of these toxicities. In a Japanese phase II study conducted in Japan to evaluate the efficacy and safety of mFOLFIRINOX in chemotherapy naïve MPC patients, mFOLFIRINOX showed comparable efficacy to, but was safer than the original regimen [8]. However, few studies have focused on the risk factors for severe neutropenia in patients treated with mFOLFIRINOX. In this retrospective study, we evaluated the incidence of FN and severe neutropenia and explored the risk factors for severe neutropenia in patients receiving treatment with mFOLFIRINOX.

Methods

This retrospective study was conducted with the approval of the ethics committee of the National Cancer Center, and in accordance with the Declaration of Helsinki (Approved No. 2014-352). We applied the opt-out method to obtain consent on this study. Consent for the treatment was obtained in writing from all patients.

Patients

The study subjects were patients with advanced pancreatic cancer who had received treatment with mFOLFIRINOX between December 2013, when FOLFIRINOX treatment was reimbursed in Japan, and December 2014, when GEM+nab-PTX treatment began to be reimbursed, at the National Cancer Center Hospital East. After treatment with GEM+nab-PTX began to be reimbursed, we administered GEM+nab-PTX to the majority of patients as first-line chemotherapy, and reserved mFOLFIRINOX only for younger patients with a good performance status. Considering this selection bias, patients with special conditions were excluded from this study. and December 2014 at the National Cancer Center Hospital

East. Patients who were homozygous for *UGT1A1**28 or *UGT1A1**6 polymorphism, or with double-variant heterozygosity for *UGT1A1**28 and *UGT1A1**6 polymorphisms were excluded from this study, because these patients have already been reported to be at a high risk of development of severe neutropenia and received irinotecan at a reduced dose [9-11].

Treatment

The mFOLFIRINOX regimen consisted of oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, and *l*-leucovorin 200 mg/m^2 on day1, followed by continuous intravenous infusion of 5-FU 2400 mg/m^2 for 46 hr. The treatment was repeated every 2 weeks. The doses of each agent could be adjusted based on the severity of adverse events. The treatment was continued until obvious disease progression or appearance of unacceptable toxicity. Prior to the treatment, a 5-HT$_3$ receptor antagonist and dexamethasone were routinely given, and a selective neurokinin 1 receptor antagonist antiemetic was given from day1-3 to prevent nausea and vomiting induced by mFOLFIRINOX. None of the patients received peg-filgrastim prophylaxis.

Assessments

The incidences of severe neutropenia and FN were determined from the electronic charts of our hospital. All adverse events, including neutropenia and FN, were graded in severity according to the Common Toxicity Criteria for Adverse Events (CTCAE version 4.0). The highest grade of toxicity during the study period was used for the analysis. The risk factors for severe neutropenia among the pretreatment patient characteristics were explored.

Relative dose intensity

The dose intensity was calculated by dividing the total dose of the agent administered by the number of weeks of treatment. The relative dose intensity (RDI) was calculated as the ratio of the actual dose intensity to that of the original regimen. The original regimen consisted of oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, continuous intravenous infusion of 5-FU 2400 mg/m^2, and bolus injection of 5-FU 400 mg/m^2.

Statistical analysis

Univariate and multivariate analysis were undertaken to evaluate the associations of the pretreatment clinical data with the incidence of severe neutropenia, and the clinical data were compared between the following two groups: patients who developed severe neutropenia (≥Grade 3) at any time during the chemotherapy and those who did not. The univariate associations between the incidence of severe neutropenia and the pretreatment clinical data were analyzed by the Chi-square test or Fisher's exact test. Multivariate logistic regression analysis was undertaken to identify factors significantly associated with the incidence of severe neutropenia. We entered all the factors that were identified as being significant by univariate analysis with a significance level of less than 0.2 into the multivariate analysis model. All the

statistical analyses were performed using R version 4.0.3 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). All reported p-values are two-sided and p <0.05 was considered as being indicative of statistical significance.

Results

A total of 129 patients received mFOLFIRINOX between December 2013 and December 2014 at the National Cancer Hospital East; of these, 7 patients (5.4%) were excluded from this study because of homozygosity for UGT1A1*28 or UGT1A1*6 or double-variant heterozygosity for UGT1A1*28 and UGT1A1*6. The remaining 122 patients were enrolled in this study. The baseline characteristics of the study subjects are summarized in Table 1. The median age of the patients was 65 years (range, 32 to 78 years), and 76 patients (62%) were male. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 81 patients (66%) and 1 in 41 patients (34%). Of the 122, 96 patients (79%) had no history of prior chemotherapy. All the patients who were enrolled in this study underwent genetic analysis for determination of the UGT1A1 genotype; 72 (59%) patients had wild-type UGT1A1, 27 (22%) were heterozygous for UGT1A1*6, and 23 (19%) were heterozygous for UGT1A1*28. The median follow-up period was 513 days [range: 307–672 days] and the median number of treatment cycles were 8 cycles [range: 1–28 cycles].

Table 1
Baseline patient characteristics

Characteristics	Number (%) of patients (N = 122)
Median age (range), years	65 (32–78)
Sex	
Male	76 (62)
Female	46 (37)
ECOG PS	
0	81 (66)
1	41 (34)
Treatment line	
1st line	96 (79)
2nd line	12 (10)
3rd line	14 (12)
Stage	
Locally advanced	26 (21)
Metastasis	77 (63)
Postoperative recurrence	19 (16)
Primary tumor location	
Head	44 (36)
Body-tail	56 (46)
None	20 (16)
Other	2 (2)
Metastatic organs	
Liver	56 (46)
Lymph node	40 (33)
Lung	21 (17)
Biliary stent	

ECOG PS, Eastern Cooperative Oncology Group performance status.

Characteristics	Number (%) of patients (N = 122)
Present	23 (19)
Absent	99 (81)
Previous history of radiotherapy	4 (3)
UGT1A1(*6/*28)	
Wild type/wild type	72 (59)
Wild type/heterozygous, n (%)	23 (19)
Heterozygous/wild type, n (%)	27 (22)
ECOG PS, Eastern Cooperative Oncology Group performance status.	

In all, 62 patients (51%) and 10 patients (8%) developed severe neutropenia and FN, respectively (Table 2). In regard to the grade of neutropenia, 51 patients (42%) developed grade 3 neutropenia, and 22 patients (18%) developed grade 4 neutropenia. Severe neutropenia were developed in 43 patients (69%) in the first cycle, 8 patients (13%) in the second cycle and 11 patients (18%) in the third or later cycles. The FN was developed in 7 patients (70%) in the first cycle and 3 patients (30%) in the second or later cycles. The RDIs of oxaliplatin, irinotecan and continuous intravenous infusion of 5-FU were 68.3%, 66.7% and 77.8%, respectively (Table 3).

Table 2
Incidence of severe neutropenia of current and previous study

Characteristics	mFOLFIRINOX, current study N = 122	mFOLFIRINOX, Japanese Phase II study [9] N = 69	FOLFIRINOX, Japanese Phase II study [6] N = 36
Grade 3–4 neutropenia, n (%)	62 (50.8)	33 (47.8)	28 (77.8)
Febrile neutropenia, n (%)	10 (8.2)	6 (8.7)	8 (22.2)

Table 3
Relative dose intensity

Characteristics	mFOLFIRINOX, current study N = 122	mFOLFIRINOX, Japanese Phase II study [9] N = 69	FOLFIRINOX, Japanese Phase II study [6] N = 36
Oxaliplatin	68.3%	76.1%	71.0%
Irinotecan	66.7%	91.4%[a]	69.6%
5-FU, bolus	-	-	15.9%
5-FU, continuous infusion	77.8%	95.4%	80.3%

[a]Relative dose intensity of irinotecan, 150 mg/m^2

To identify the risk factors for severe neutropenia, the associations between the incidence of grade 3/4 neutropenia and the patient characteristics were analyzed by univariate analysis (Table 4). The patients were classified into the “Non-grade 3/4 neutropenia” group (60 patients, 49%) and the “Grade 3/4 neutropenia” group (62 patients, 51%). The univariate analysis identified the following factors as being significant, with p-values of less than 0.2: female sex, heterozygosity for UGT1A1 UGT1A1*28 or UGT1A1*6, and a low baseline white blood cell (WBC) count, low baseline neutrophil count, low hemoglobin level, high serum alanine aminotransferase level, high serum total bilirubin level, and low serum albumin level at the study baseline. When these factors were entered into a multivariate analysis, only a low WBC count (odds ratio [OR], 14.50; 95% confidence interval (CI), 3.27-111.14; p = 0.002) and presence of heterozygosity for UGT1A1*28 or UGT1A1*6 polymorphism (OR, 2.84; 95% CI, 1.18–7.17; p = 0.023) were identified as independent risk factors (Table 4). Severe neutropenia was observed in 22 (91.7%) of the patients with low WBC count at the baseline, 30 (60%) of the patients with UGT1A1 heterozygous for UGT1A1*28 or UGT1A1*6 polymorphism, and 10 (100.0%) of the patients had both of the above factors.

Table 4
Risk factors for severe neutropenia

Variables		Number (%) of patients with severe neutropenia	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yr)	< 65	25 (40.3)	1.57 (0.73–3.45)	0.209		
	≥ 65	37 (59.7)				
Sex	Male	35 (56.5)	1.65 (0.75–3.74)	0.176	1.46 (0.56–3.86)	0.436
	Female	27 (43.5)				
ECOG-PS	0	42 (67.7)	0.89 (0.39–2.01)	0.749		
	1	20 (32.3)				
UGT1A1 heterozygous	No	32 (51.6)	1.87 (0.85–4.17)	0.091	2.84 (1.18–7.17)	0.023
	Yes	30 (48.4)				
Peritoneal dissemination	No	46 (74.2)	0.70 (0.29–1.63)	0.362		
	Yes	16 (25.8)				
Biliary stent	Absent	48 (77.4)	1.65 (0.60–4.74)	0.285		
	Preset	14 (22.6)				

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; WBC, white blood cell; Neu, neutrophil count; Lym, lymphocyte count; Hb, hemoglobin level; Plt, platelet count; CRP, serum level of C-reactive protein; AST, serum level of aspartate aminotransferase; ALT, serum level of alanine aminotransferase; T-Bil, serum level of total bilirubin; Alb, serum level of albumin; CCr, Creatinine clearance

[a] The median value was set as the cut-off value.

[b] The lower limit of normal was set as the cut-off value.

[c] The upper limit of normal was set as the cut-off value.

Variables		Number (%) of patients with severe neutropenia	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Liver metastasis	No	31 (50.0)	1.40 (0.64–3.05)	0.356		
	Yes	31 (50.0)				
Lymph node metastasis	No	44 (71.0)	0.71 (0.31–1.62)	0.369		
	Yes	18 (29.0)				
Stage	III	13 (21.0)	1.04 (0.40–2.72)	0.925		
	IV	49 (79.0)				
Baseline CEA (ng/mL) [a]	< 5.6	30 (48.4)	1.14 (0.53–2.46)	0.717		
	≥ 5.6	32 (51.6)				
Baseline CA19-9 (U/mL) [a]	< 391.1	34 (54.8)	0.68 (0.31–1.46)	0.277		
	≥ 391.1	28 (45.2)				
Treatment line	1st line	50 (80.6)	0.79 (0.30–2.06)	0.592		
	2nd line or later	12 (19.4)				

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; WBC, white blood cell; Neu, neutrophil count; Lym, lymphocyte count; Hb, hemoglobin level; Plt, platelet count; CRP, serum level of C-reactive protein; AST, serum level of aspartate aminotransferase; ALT, serum level of alanine aminotransferase; T-Bil, serum level of total bilirubin; Alb, serum level of albumin; CCr, Creatinine clearance

[a] The median value was set as the cut-off value.

[b] The lower limit of normal was set as the cut-off value.

[c] The upper limit of normal was set as the cut-off value.

Variables		Number (%) of patients with severe neutropenia	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Previous history of radiation therapy	No	60 (96.8)	0.97 (0.07–13.75)	1.000		
	Yes	2 (3.2)				
Baseline WBC (/mm^3)[b]	≥ 4500	40 (64.5)	15.64 (3.52-144.58)	< 0.001	14.50 (3.27-111.14)	0.002
	< 4500	22 (35.5)				
Baseline Neu (/mm^3)[b]	≥ 2160	54 (87.1)	8.62 (1.10-393.53)	0.033	3.19 (0.22–84.74)	0.406
	< 2160	8 (12.9)				
Baseline Lym (/mm^3)[b]	≥ 1125	42 (67.7)	0.95 (0.42–2.17)	0.899		
	< 1125	20 (32.3)				
Baseline Hb (g/dL)[b]	≥ 13 (male),12 (female)	26 (41.9)	1.80 (0.83–3.95)	0.104	1.54 (0.58–4.12)	0.386
	< 13(male),12 (female)	36 (58.1)				
Baseline Plt[b]	≥ 120,000	55 (88.7)	2.40 (0.51–15.12)	0.323		
	< 120,000	7 (11.3)				

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; WBC, white blood cell; Neu, neutrophil count; Lym, lymphocyte count; Hb, hemoglobin level; Plt, platelet count; CRP, serum level of C-reactive protein; AST, serum level of aspartate aminotransferase; ALT, serum level of alanine aminotransferase; T-Bil, serum level of total bilirubin; Alb, serum level of albumin; CCr, Creatinine clearance

[a] The median value was set as the cut-off value.

[b] The lower limit of normal was set as the cut-off value.

[c] The upper limit of normal was set as the cut-off value.

Variables		Number (%) of patients with severe neutropenia	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p-value	OR (95% CI)	p-value
Baseline CRP (mg/dL)[c]	≥ 0.3	26 (41.9)	1.48 (0.68–3.22)	0.282		
	< 0.3	36 (58.1)				
Baseline AST (IU/L)[c]	< 40	54 (87.1)	0.60 (0.19–1.74)	0.290		
	≥ 40	8 (12.9)				
Baseline ALT (IU/L)[c]	< 40	52 (83.9)	0.45 (0.17–1.16)	0.069	0.62 (0.22–1.72)	0.368
	≥ 40	10 (16.1)				
Baseline T-Bil (mg/dl)[c]	< 1.2	55 (88.7)	3.66 (0.66–37.57)	0.164	3.53 (0.68–27.15)	0.162
	≥ 1.2	8 (11.3)				
Baseline Alb (g/dL)[b]	≥ 3.8	35 (56.5)	1.95 (0.85–4.58)	0.083	2.56 (0.91–7.45)	0.077
	< 3.8	25 (40.3)				
Baseline CCr (mL/min)	≥ 60	52 (83.9)	1.72 (0.52–6.21)	0.316		
	< 60	10 (16.1)				

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; WBC, white blood cell; Neu, neutrophil count; Lym, lymphocyte count; Hb, hemoglobin level; Plt, platelet count; CRP, serum level of C-reactive protein; AST, serum level of aspartate aminotransferase; ALT, serum level of alanine aminotransferase; T-Bil, serum level of total bilirubin; Alb, serum level of albumin; CCr, Creatinine clearance

[a] The median value was set as the cut-off value.

[b] The lower limit of normal was set as the cut-off value.

[c] The upper limit of normal was set as the cut-off value.

Discussion

FN is associated with an increased risk of prolonged hospitalization, worse clinical outcomes, and life-threatening complications. Chemotherapeutic regimens that are associated with a high incidence of FN (> 20%) in chemo-naïve patients are considered as being high-risk regimens, and prophylactic administration of G-CSF is recommended in such patients [12]. Therefore, mFOLFIRINOX was devised to reduce the incidence of toxicities, including neutropenia and FN, associated with FOLFIRINOX. In this study, we retrospectively evaluated the incidence of FN and severe neutropenia associated with mFOLFIRINOX therapy, in order to identify the risk factors for severe neutropenia. The single-institution study was undertaken using the same unified method for tumor staging and identical treatment regimens and the same protocol for follow-up of blood sampling and administration of granulocyte colony stimulating factor products, and we provided supportive care throughout, which enabled us to confirm important predictive factors.

The patient selection criteria for this study were broader than those of previous Japanese phase II studies, because this retrospective study was conducted in clinical practice. But, the patients homozygosity for UGT1A1*28 or UGT1A1*6 or double-variant heterozygosity for UGT1A1*28 and UGT1A1*6 were excluded from this analysis, because these patients treated with reduced dose of FOLFIRINOX in clinical practice. As compared to the Japanese phase II study of FOLFIRINOX, the median age of the enrolled patients was higher (65.0 years vs. 61.5 years) and the treatment line was not limited to 1st line treatment in this study. Nonetheless, the incidence of severe neutropenia and FN were lower than those reported for FOLFIRINOX [6], and the results were consistent with those in the Japanese phase II study of mFOLFIRINOX [8]. The RDIs of oxaliplatin, irinotecan and continuous intravenous infusion of 5-FU in this study were comparable to those reported for FOLFIRINOX [6] (Table 3). In addition, in 69% and 70% of cases, respectively, the severe neutropenia and FN occurred during the first cycle of treatment in this study. In the Japanese phase II study of FOLFIRINOX [6], FN only occurred during the first cycle of treatment, so that the tendency seemed to be similar. Even in modified regimen, it is important to pay careful attention to severe neutropenia and FN especially during the first cycle and to undergo appropriate dose modification against the toxicities in the subsequent cycles.

In this study, we found that a low baseline WBC count and presence of heterozygosity for *UGT1A1**28 or *UGT1A1**6 polymorphism were significant independent risk factors for the development of severe neutropenia during treatment with mFOLFIRINOX. The NCCN guideline mentions higher age, history of prior chemotherapy or radiotherapy, preexisting infection or neutropenia, tumor involvement of the bone marrow, poor PS, and comorbidities including renal and liver dysfunction [13]. In this study, the baseline WBC count was associated with the risk of severe neutropenia, this result was consistent with other chemotherapeutic regimens in previous studies [14–17]. On the other hand, we considered that low baseline neutrophil and low baseline WBC counts were cofounding factors, and low baseline neutrophil count was identified as one of the significant risk factors by univariate, but not by multivariate analysis.

UGT1A1 is known to be involved in the metabolism of SN-38, an active metabolite of irinotecan, and double-variants of *UGT1A1* have been often reported to be risk factors for severe myelosuppression [10]. There are significant racial differences in the distribution of *UGT1A1* polymorphisms among Asians, Caucasians, and Africans. The frequency of *UGT1A1**28 in Asians (16%) is one-third that in Caucasians (29%-45%), and *UGT1A1**6 is not detected at all in Caucasians or Africans, but is as frequent as the *28 allele in Asians (15%-20%) [18]. Several studies have suggested that the incidence of severe neutropenia is significantly higher in patients with double-variant *UGT1A1**28 and *6 heterozygosity than in those with the wild-type genotype. A meta-analysis suggested that the incidence of severe neutropenia is significantly higher in patients who heterozygous for *UGT1A1**28 or *6 polymorphism than in patients with the wild-type genotype [19, 20]. A previously reported prospective study on pancreatic cancer showed that the incidence of grade 3–4 hematological adverse events was higher in patients who were heterozygous for UGT1A1 *6 or UGT1A1 *28 than in patients with wild-type UGT1A1, although the difference did not reach statistical significance. However, the study suggested that the incidence of diarrhea was significantly higher in patients with heterozygous polymorphisms of UGT1A1*6 or *28 than in patients with the wild-type genotype [21]. Therefore, there appears to be convincing evidence to suggest that patients who are heterozygous for *UGT1A1**6 or *28 polymorphism are at an increased risk for irinotecan toxicity as compared to patients with wild-type *UGT1A1*.

There were some limitations of this study. Firstly, the relatively small number of patients and there were only 27 patients who were heterozygous for *UGT1A1**28 or *UGT1A1**6 in the study made it difficult to draw any definitive conclusions. Furthermore, the study was a single-center and retrospective study, influenced by local individual clinician practices. Therefore, further clinical investigation, such as a multicenter trial is warranted to evaluate the risk factors for severe neutropenia associated with mFOLFIRINOX therapy in patients. Secondly, the safety data of mFOLFIRINOX were not evaluated in patients who were homozygous for *UGT1A1**28 or *UGT1A1**6 or heterozygous for both *UGT1A1**6 and *UGT1A1**28 in this study. However, a multicenter retrospective study of FOLFIRINOX in advanced pancreatic cancer patients with double-variant type *UGT1A1**28 and *6 polymorphism was conducted by our colleagues and they recommend that the initial dose of irinotecan should be further reduced to ≤ 120 mg/m^2 of body surface area in such patients [22].

In conclusion, the incidences of severe neutropenia and FN were lower in the patients who received mFOLFIRINOX as compared to those reported for patients treated with FOLFIRINOX, despite the absence of significant differences in the relative dose intensities of the component drugs. The risk factors for severe neutropenia in patients receiving mFOLFIRINOX were a low baseline WBC count and heterozygosity for *UGT1A1**28 or *UGT1A1**6 polymorphism. Therefore, mFOLFIRINOX should be administered with caution in patients with these risk factors.

Declarations

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Author Contributions:

A.I. and M.I. designed the original concept of the study, discussed and modified the study, collection and/or assembly of data, interpreted data, created the first manuscript draft, revised the manuscript drafts, and provided final approval of the manuscript to be published.

M.T., K.W., H.T., and S.M. helped conceive the design of the study, collection and/or assembly of data, interpreted data, critically reviewed the manuscript drafts, and provided final approval of the manuscript to be published.

Competing Interests:

M.I reports personal fees and other from Chugai, other from Yakult, personal fees and other from Nihon Servier, other from Ono, other from Bristol-Myers Squibb, personal fees from Taiho, personal fees from AstraZeneca, other from Novartis, and other from Delta-Fly Pharma, during the conduct of the study; personal fees and other from Bayer, personal fees and other from Eisai, other from Merck Serono, personal fees and other from MSD, other from J-Pharma, personal fees from Teijin Pharma, personal fees from Astellas, personal fees and other from EA Pharma, other from Pfizer, other from Chiome Bioscience, personal fees and other from ASLAN, personal fees from Sumitomo Dainippon, personal fees from Gilead, personal fees from Otsuka, other from GlaxoSmithKline, outside the conduct of the study. The other authors declare no potential conflict of interest.

Data Availability:

The dataset is not publicly available because the ethical review and the informed consent for public release was not obtained.

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