Impact of UGT1A1 genetic polymorphism on toxicity in unresectable pancreatic cancer patients undergoing FOLFIRINOX

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Studies have indicated an association between UDP-glucuronosyltransferase-1A1 (UGT1A1) genetic polymorphisms and irinotecan-induced toxicity. We undertook this study to investigate the association between UGT1A1 genetic polymorphisms and toxicity in patients treated with the FOLFIRINOX (comprising oxaliplatin, irinotecan, fluorouracil, and leucovorin) chemotherapy regimen in the JASPAC 06 study. Patients screened for UGT1A1*6 and UGT1A1*28, and treated with either the original FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 200 mg/m², bolus 5-fluorouracil [5-FU] 400 mg/m², and continuous 5-FU 2400 mg/m²) or a
modified FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 150 mg/m², leucovorin 200 mg/m², and continuous 5-FU 2400 mg/m²) as first-line chemotherapy were included. Of 199 patients eligible for this analysis, 79 patients were treated with the original FOLFIRINOX regimen and 120 patients were treated with the modified FOLFIRINOX regimen. In the original FOLFIRINOX group, 54 were UGT1A1 WT, and 25 were UGT1A1 heterozygous type (−/∗6, 12 patients; −/∗28, 13 patients). In the modified FOLFIRINOX group, 64 were UGT1A1 WT and 56 were UGT1A1 heterozygous type (−/∗6, 33 patients; −/∗28, 23 patients). In the original FOLFIRINOX group, the incidence of diarrhea was significantly higher among patients with UGT1A1 heterozygous type than among those with UGT1A1 WT and the incidence of leukopenia and diarrhea was significantly higher among patients with UGT1A1 −/∗6 than among those with UGT1A1 −/∗28. Patients with UGT1A1 heterozygous type, especially those with UGT1A1 −/∗6, tended to show a higher incidence rate of severe adverse events, but this was not statistically significant. However, for patients who received the modified FOLFIRINOX, there was no difference in the frequency of adverse events due to UGT1A1 status. In conclusion, patients with heterozygous UGT1A1 polymorphisms treated with the original FOLFIRINOX regimen experienced severe toxicity more frequently than patients with WT UGT1A1.

**KEYWORDS**

chemotherapy, FOLFIRINOX, pancreatic cancer, toxicity, UGT1A1

## 1 | INTRODUCTION

Pancreatic cancer is one of the most lethal types of common cancer and the eighth and ninth leading cause of cancer-related death among men and women worldwide, respectively. A randomized phase II/III study found that improvement in overall survival, progression-free survival, and response rate among patients with metastatic pancreatic cancer were significantly greater among patients given a combination chemotherapy regimen comprising oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) compared to those treated with gemcitabine. However, a higher incidence of adverse events was associated with the FOLFIRINOX regimen.2 To improve tolerability of the FOLFIRINOX regimen, a modified version has been used in practice. Several reports have suggested improved safety and maintained efficacy under the modified FOLFIRINOX regimen.3,4

Irinotecan is a prodrug, and its active metabolite SN-38 shows antitumor activity and toxicity.5,6 SN-38 is inactivated into SN-38 glucuronide mainly by UDP-glucuronosyltransferase 1A1 (UGT1A1).7 Genetic polymorphisms in UGT1A1, such as UGT1A128 and UGT1A1∗6, contribute to interpatient variability in the pharmacokinetics and toxicity of irinotecan, particularly severe neutropenia. Decreased UGT1A1 activity is commonly attributed to the insertion of TA in the TATA box of the UGT1A1 gene promoter, and this polymorphism is named UGT1A1∗28.8 Several meta-analyses have examined the impact of the *28 allele on irinotecan-based therapy toxicity.9-11 A further polymorphism, UGT1A1∗6, characterized by a single nucleotide replacement in exon 1 of the UGT1A1 gene, is the most frequent and important polymorphism among the Asian population and is rarely found among Caucasians.12 Many studies have reported a significant association between the UGT1A1∗6/*6 type and severe neutropenia, although no association was found with UGT1A1 WT.13-17 UGT1A1∗28 occurs with a frequency of 26%-31% among Caucasians, 42%-56% among African Americans, and only 9%-16% among Asians.13,19 UGT1A1∗6 has allele frequencies of 0%, 13%, 23%, and 23% among German, Japanese, Korean, and Chinese populations, respectively.20 In Japan, three genotypes were identified based on the following types of UGT1A1∗6 and ∗28 genetic polymorphisms: WT (∗/∗), heterozygous type (∗/∗6 and ∗/∗28), and homozygous type (∗/∗6, ∗/∗28). Compound heterozygous type (∗/∗28) was classified as homozygous based on the results of previous studies.14,21,22

Studies have shown an association between UGT1A1 genetic polymorphisms and irinotecan-induced toxicity, although the only cancer type specifically investigated was colorectal cancer. The association between UGT1A1 genetic polymorphisms and FOLFIRINOX-induced toxicity remains unclear. Furthermore, to our knowledge, there are few studies on the association between toxicity and heterozygous type or WT,10,12,16,17,23 nevertheless the frequency of heterozygous UGT1A1 polymorphisms is approximately 40%.24 We undertook this
study to investigate the association between UGT1A1 genetic polymorphisms and toxicity in patients treated with FOLFIRINOX in the JASPAC 06 study.

2 MATERIALS AND METHODS

2.1 Patients

An exploratory analysis was carried out using pooled data from the JASPAC 06 study, a nationwide multicenter observational study of FOLFIRINOX in patients with unresectable and recurrent pancreatic cancer. The JASPAC 06 study was undertaken to evaluate the safety of FOLFIRINOX therapy in clinical practice in Japan. The subjects were patients with unresectable or recurrent pancreatic cancer given FOLFIRINOX therapy at 27 institutions in Japan over a 1-year period, starting on December 20, 2013. All patients at each institution were registered.

This study included patients who were screened for UGT1A1 genetic polymorphisms and given either the standard FOLFIRINOX regimen (oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 200 mg/m², bolus 5-fluorouracil [5-FU] 400 mg/m², and continuous 5-FU 2400 mg/m², every 2 weeks; original FOLFIRINOX group) or the modified regimen (Oxaliplatin 85 mg/m², Irinotecan 150 mg/m², Leucovorin 200 mg/m², and continuous 5-FU 2400 mg/m², every 2 weeks; modified FOLFIRINOX group) as first-line chemotherapy. Patients with homozygous (*6/*6, *28/*28) or compound heterozygous (*6/*28) UGT1A1 polymorphisms were excluded. This study protocol was approved by the Shizuoka Cancer Center Institutional Review Board (Shizuoka, Japan) and carried out in accordance with the Ethical Guidelines for Epidemiological Research. This trial was registered at the UMIN Clinical Trials Registry as UMIN000014658.

2.2 Evaluation

Toxicity was graded by the Common Toxicity Criteria for Adverse Events version 4.0.

2.3 Statistical analysis

Comparisons between categorical variables were carried out using Fisher’s exact test. Median values of variables were compared using the Mann–Whitney U test. A P-value < .05 was considered statistically significant. Statistical analysis was undertaken using the software EZR version 1.32 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3 RESULTS

3.1 Patient selection and characteristics

Of the 399 eligible patients in the JASPAC 06 study, 200 patients were excluded for the following reasons: previous chemotherapy (n = 146), use of a different chemotherapy regimen that is reduced more than the modified FOLFIRINOX regimen (n = 50), lack of genetic testing (n = 11), and UGT1A1 homozygous type (n = 9) or compound heterozygous type (n = 6) polymorphisms; there were some overlaps between these criteria (Figure 1). Finally, 199 patients were analyzed in the present study. Of these, 79 were treated with the original FOLFIRINOX and 120 patients were treated with the modified FOLFIRINOX therapy as initial treatment. Patient characteristics are shown in Table 1. Of the 199 patients, 118 (59%) were WT for UGT1A1 polymorphisms, 45 (23%) were heterozygous for UGT1A1*6, and 36 (18%) were heterozygous for UGT1A1*28. In the original FOLFIRINOX group, 54 (68%) patients had UGT1A1 WT, and 25 (32%) had UGT1A1 heterozygous type (*6/*28 in 12 and *28/*28 in 13 patients). In the modified FOLFIRINOX group, 64 (53%) patients had UGT1A1 WT, and 56 (47%) had UGT1A1 heterozygous type (*6/*28 in 23 patients). In each treatment group, most patient characteristics were comparable between the heterozygous type and WT.

3.2 Incidence of grade III-IV adverse events according to UGT1A1 status in each cycle

Incidence of grade III-IV major adverse events according to UGT1A1 status (WT vs heterozygous type vs *6/*6 type vs *28/*28 type) among patients given either the original FOLFIRINOX or the modified FOLFIRINOX regimen are summarized in Figures 2 and 3, respectively. Cycle 1 had one of the highest incidences of adverse events. In the modified FOLFIRINOX group, the incidence of grade III-IV adverse events tended to be lower than in the original FOLFIRINOX group.
TABLE 1  Characteristics of 199 patients with unresectable pancreatic cancer treated with oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX)

|                        | Original FOLFIRINOX (n = 79) |                     | Modified FOLFIRINOX (n = 120) |                     |
|------------------------|------------------------------|---------------------|-------------------------------|---------------------|
|                        | Wild (n = 54)                | Hetero (n = 25)     | Wild (n = 64)                 | Hetero (n = 56)     |
|                        | n (%)                        | n (%)               | n (%)                         | n (%)               |
| **Median age, years (range)** | 60.5 (41-72)                | 60 (43-74)          | 62.5 (34-75)                  | 62 (31-74)          |
| **Gender**             |                              |                     |                               |                     |
| Male                   | 39 (72)                      | 15 (60)             | 44 (69)                       | 38 (68)             |
| Female                 | 15 (28)                      | 10 (40)             | 20 (31)                       | 18 (32)             |
| **ECOG PS**            |                              |                     |                               |                     |
| 0                      | 31 (57)                      | 13 (52)             | 49 (77)                       | 39 (70)             |
| 1                      | 23 (43)                      | 12 (48)             | 14 (22)                       | 17 (30)             |
| 2                      | 0 (0)                        | 0 (0)               | 1 (1)                         | 0 (0)               |
| **Disease state**      |                              |                     |                               |                     |
| Recurrence             | 1 (2)                        | 0 (0)               | 3 (5)                         | 1 (2)               |
| LA                     | 17 (32)                      | 9 (36)              | 15 (23)                       | 11 (20)             |
| Metastatic             | 36 (67)                      | 16 (64)             | 46 (72)                       | 44 (78)             |
| **UGT1A1**             |                              |                     |                               |                     |
| −/−                    | 54 (100)                     |                     | 64 (100)                      |                     |
| −/*6                   | –                             | 12 (48)             | –                             | 33 (59)             |
| −/*28                  | –                             | 13 (52)             | –                             | 23 (41)             |

LA, locally advanced; PS, performance status.

FIGURE 2  Incidence of grade III-IV major adverse events in each cycle according to UGT1A1 status (WT vs heterozygous type vs −/*6 type vs −/*28 type) among 199 patients with unresectable pancreatic cancer treated with the original regimen of oxaliplatin, irinotecan, fluorouracil, and leucovorin.
3.3 | UGT1A1 WT vs heterozygous type

Treatment delivery and incidence of grade III-IV adverse events according to UGT1A1 status (WT vs heterozygous type) among patients treated with either the original FOLFIRINOX or the modified FOLFIRINOX regimen are summarized in Table 2. In the original FOLFIRINOX group, the incidence of grade III-IV diarrhea was significantly higher among patients with heterozygous type than among those with WT (20% vs 4%, P = .03). The incidence of other major grade III-IV adverse events tended to be higher among patients with heterozygous type than among those with WT, but this was not statistically significant (leukopenia 44% vs 28%, P = .20; neutropenia 68% vs 59%, P = .62; grade IV neutropenia 40% vs 24%, P = .19; febrile neutropenia 40% vs 24%, P = .19; anorexia 24% vs 9%, P = .09). In the modified FOLFIRINOX group, the incidence of grade III-IV adverse events was lower than in the original FOLFIRINOX group, and there was no difference between patients with WT and heterozygous type.

3.4 | UGT1A1 −/*6 vs −/*28 type

Treatment delivery and incidence of grade III-IV adverse events according to UGT1A1 status (−/*6 vs −/*28 type) among patients treated with either the original FOLFIRINOX or the modified FOLFIRINOX regimen are summarized in Table 4. In the original FOLFIRINOX group, the incidence of grade III-IV leukopenia and diarrhea was significantly higher among patients with UGT1A1 −/*6 than among those with UGT1A1 −/*28 (leukopenia 75% vs 23%, P = .04; diarrhea 42% vs 0%, P = .01). The incidence of other major grade III-IV adverse events tended to be higher among patients with UGT1A1 −/*6 than among those with UGT1A1 −/*28, but this was not statistically significant (neutropenia 83% vs 54%, P = .20; grade IV neutropenia 50% vs 31%, P = .43; febrile neutropenia 50% vs 31%, P = .43; nausea 17% vs 0%, P = .59; anorexia 24% vs 9%, P = .38). In the modified FOLFIRINOX group, the incidence of adverse events was comparable among patients with UGT1A1 −/*6 and −/*28.

Incidence of grade III-IV adverse events according to UGT1A1 status (−/*6 vs −/*28 type) in cycle 1 among patients treated with either the original FOLFIRINOX or the modified FOLFIRINOX regimen are summarized in Table 5. In the original FOLFIRINOX group, the incidence of grade III-IV leukopenia and neutropenia in cycle 1 was significantly higher among patients with UGT1A1 −/*6 than among those with UGT1A1 −/*28 (leukopenia 67% vs 15%, P = .015; neutropenia 67% vs 15%, P = .015). The incidence of other major grade III-IV
### TABLE 2  Treatment delivery and adverse events among 199 patients with unresectable pancreatic cancer treated with oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX), according to UGT1A1 (WT vs heterozygous)

| CTCAE version 4.0 | Original FOLFIRINOX (n = 79) |  | Modified FOLFIRINOX (n = 120) |  |
|-------------------|--------------------------------|-----------------|--------------------------------|-----------------|
|                   | WT (n = 54) | Hetero (n = 25) | P value | WT (n = 64) | Hetero (n = 56) | P value |
| Treatment delivery |                |                |         |                |                |         |
| Median number of treatment cycles (range) | 7 (1-13) | 4 (1-12) | 0.11 | 8 (1-14) | 9 (1-13) | 0.65 |
| Dose reduction in cycle ≥ 2 | 42 (78) | 20 (80) | 1.00 | 48 (75) | 38 (68) | .42 |
| Adverse events (grade III-IV) |   |   |         |   |   |         |
| Hematological |   |   |         |   |   |         |
| Leukopenia | 15 (28) | 11 (44) | .20 | 14 (22) | 15 (27) | .67 |
| Neutropenia | 32 (59) | 17 (68) | .62 | 28 (44) | 28 (50) | .58 |
| Neutropenia (grade IV) | 13 (24) | 10 (40) | .19 | 10 (16) | 11 (20) | .63 |
| Anemia | 2 (4) | 3 (12) | .32 | 2 (3) | 3 (5) | .66 |
| Thrombocytopenia | 2 (4) | 1 (4) | 1.00 | 0 (0) | 0 (0) | 1.00 |
| Non-hematological |   |   |         |   |   |         |
| Febrile neutropenia | 13 (24) | 10 (40) | .19 | 3 (5) | 4 (7) | .70 |
| Fever | 2 (4) | 1 (4) | 1.00 | 0 (0) | 1 (2) | 1.00 |
| Nausea | 2 (4) | 3 (12) | .32 | 4 (6) | 1 (2) | .37 |
| Vomiting | 1 (2) | 2 (8) | .23 | 0 (0) | 1 (2) | .47 |
| Diarrhea | 2 (4) | 5 (20) | .03 | 10 (16) | 4 (7) | .17 |
| Fatigue | 2 (4) | 1 (4) | 1.00 | 1 (2) | 1 (2) | 1.00 |
| Anorexia | 5 (9) | 6 (24) | .09 | 9 (14) | 5 (9) | .41 |
| PSN | 1 (2) | 0 (0) | 1.00 | 4 (6) | 1 (2) | .37 |
| Oral mucositis | 0 (0) | 0 (0) | 1.00 | 0 (0) | 0 (0) | 1.00 |

CTCAE, Common Toxicity Criteria for Adverse Events; PSN, peripheral sensory neuropathy.

### TABLE 3  Adverse events during cycle 1 of treatment with oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) in 199 patients with unresectable pancreatic cancer, according to UGT1A1 (WT vs heterozygous)

| CTCAE version 4.0 | Original FOLFIRINOX (n = 79) |  | Modified FOLFIRINOX (n = 120) |  |
|-------------------|--------------------------------|-----------------|--------------------------------|-----------------|
|                   | Wild (n = 54) | Hetero (n = 25) | P value | Wild (n = 64) | Hetero (n = 56) | P value |
| Adverse events (grade III-IV) |   |   |         |   |   |         |
| Leukopenia | 12 (22) | 10 (40) | .11 | 11 (17) | 10 (18) | 1.00 |
| Neutropenia | 23 (43) | 10 (40) | 1.00 | 18 (28) | 21 (38) | .33 |
| Neutropenia (grade IV) | 10 (19) | 8 (32) | .25 | 8 (13) | 8 (14) | .79 |
| Febrile neutropenia | 7 (13) | 6 (24) | .33 | 2 (3) | 3 (5) | .67 |
| Diarrhea | 2 (4) | 1 (4) | 1.00 | 5 (9) | 3 (5) | .72 |

CTCAE, Common Toxicity Criteria for Adverse Events.

Adverse events in cycle 1 tended to be higher among patients with heterozygous type than among those with WT, but this was not statistically significant (grade IV neutropenia 50% vs 15%, $P = .097$; febrile neutropenia 42% vs 8%, $P = .073$; diarrhea 8% vs 0%, $P = .48$). In the modified FOLFIRINOX group, the incidence of adverse events in cycle 1 was comparable among patients with UGT1A1 −/∗6 and −/∗28.

### DISCUSSION

The present study is the first report investigating the association between UGT1A1 genetic polymorphisms, specifically UGT1A1*6 and UGT1A1*28 heterozygosity, and toxicity among Japanese patients with pancreatic cancer treated with FOLFIRINOX.
Conversely, there are few studies investigating the association between toxicity and UGT1A1 heterozygous type (UGT1A1*6 or UGT1A1*28). A meta-analysis by Liu et al reported that patients with UGT1A1*28 had a significantly higher rate of severe neutropenia than patients with UGT1A1*6 among colorectal cancer treated with irinotecan combination regimens (odds ratio = 1.90; 95% confidence interval, 1.44-2.51; P < .01). Furthermore, reports have indicated a significantly higher incidence of severe neutropenia among patients with UGT1A1*28. However, it is unclear whether the initial dose reduction of irinotecan was appropriate for individuals with UGT1A1*6 or UGT1A1*28.

Our study showed that in the original FOLFIRINOX group the incidence of diarrhea was significantly higher among patients with UGT1A1 heterozygous type than among those with UGT1A1 WT.
and the incidence of leukopenia and diarrhea was significantly higher among patients with UGT1A1 */6 than among those with UGT1A1 */28. In addition, we analyzed the incidence of grade III-IV adverse events according to UGT1A1 status in each treatment cycle. Cycle 1 had one of the highest incidences of adverse events regardless of UGT1A1 status or treatment regimen (original FOLFIRINOX or modified FOLFIRINOX). One of the reasons is that dose reduction of chemotherapeutic drugs was undertaken due to toxicity. As several factors such as dose modification or treatment course influence the incidence of adverse events, we attempted to analyze the incidence of adverse events in cycle 1 to adjust these factors. The incidence of leukopenia and neutropenia in cycle 1 was significantly higher among patients with UGT1A1 */6 than among those with UGT1A1 */28.

Patients with UGT1A1 heterozygous type, especially those with UGT1A1 */6 tended to show a higher incidence rate of severe adverse events regardless of treatment cycle in the original FOLFIRINOX group. Although there was not a significant difference, probably owing to the small patient population, careful attention should be paid to this trend.

Toxicity among patients with UGT1A1 WT was comparable to that reported in the phase II FOLFIRINOX trial in Japan; however, among patients with UGT1A1 heterozygous type, grade III-IV febrile neutropenia, anorexia, and diarrhea occurred more frequently (40% vs 22.2%, 24% vs 11.1%, and 20% vs 8.3%, respectively).27

Furthermore, the tendency that patients with UGT1A1 */6 experienced severe toxicity more frequently than those with UGT1A1 */28 in the original FOLFIRINOX group is consistent with previous reports. Several studies showed that the UGT1A1*/6 variant, but not the UGT1A1*28 variant, was associated with severe neutropenia or diarrhea.13,28,29

The FOLFIRINOX regimen, using the same doses and schedule as in the PRODIGE 4/ACCORD 11 trial, was approved in Japan for advanced pancreatic cancer in 2013. However, hematological toxicity in the phase II FOLFIRINOX trial for Japanese patients was reported to be higher than in the PRODIGE 4/ACCORD 11 trial.2,27 This outcome might have been caused by the fact that patients with the UGT1A1*6 variant were analyzed in addition to those with the UGT1A1*28 variant.

Our study also showed that, in the modified FOLFIRINOX group, the incidence of adverse events was comparable among patients with UGT1A1 heterozygous type and UGT1A1 WT or among patients with UGT1A1 */6 and */28 regardless of treatment cycle. In addition, severe hematological adverse events occurred less frequently among patients in the modified FOLFIRINOX group than among those in the original FOLFIRINOX group.

These findings might be due to the initial irinotecan dose reduction. Several meta-analyses reported that UGT1A1 *28*/28 was associated with an increased risk of neutropenia at high doses (180-350 mg/m²) of irinotecan, although this association has not been clearly established at low doses (<150 mg/m²).9,11 However, further meta-analysis evaluating predominantly Asian populations reported that patients with UGT1A1 *6*/6 or UGT1A1 */6 had an increased incidence of severe neutropenia and this was associated with any dose of irinotecan.20 Although there are contradictory reports, our findings suggest that the association between increased risk of adverse events and UGT1A1 status might not be established in patients treated with low-dose irinotecan.

In clinical practice in Japan, the initial irinotecan dose reduction to 150 mg/m² and the omission of the 5-FU bolus are widely used as the modified FOLFIRINOX regimen among patients with advanced pancreatic cancer, based on experience using FOLFIRI for patients with colorectal cancer. The phase II trial to evaluate this modified FOLFIRINOX regimen showed equivalent efficacy and a reduction in hematological toxicity compared with the phase II study of the original FOLFIRINOX regimen.27,31 We postulate that the optimal dose of irinotecan (180 mg/m² as original FOLFIRINOX regimen or 150 mg/m² as modified FOLFIRINOX regimen) for patients with UGT1A1 heterozygous type undergoing FOLFIRINOX therapy could be determined from the results of this study.

The present study has several limitations. First, the effectiveness of FOLFIRINOX therapy was not evaluated in our study. We investigated subjects with recurrent, locally advanced, and metastatic pancreatic cancer, and these were classified into 3 groups for analysis. Effectiveness might not be accurate due to the small number of patients. Second, patients with homozygous or compound heterozygous UGT1A1 polymorphisms were excluded. In the JASPAC 06 study, there were 15 patients with homozygous or compound heterozygous UGT1A1 polymorphisms, and only 5 patients underwent either modified or original FOLFIRINOX therapy as the primary treatment. The other 10 patients did not satisfy the eligibility criteria in this study, because the initial irinotecan dose reduction to less than 150 mg/m² was undertaken to reduce the toxicity. The characteristics and incidence of adverse events of these 5 patients are shown in Table S1. Finally, the statistically significant difference in the incidence of severe adverse events was observed only in diarrhea when comparing heterozygous and WT. Similarly, when comparing UGT1A1 */6 and UGT1A1 */28, significant difference was limited in leukopenia and diarrhea. This is probably due to the small number of patients in each group.

Despite these limitations, our study evaluated the safety of the FOLFIRINOX regimen among patients with UGT1A1 heterozygous type in detail, by unifying the initial dose of FOLFIRINOX regimen and excluding the effects of previous treatment. This study is important because it is the first study to investigate the association between severe adverse events in patients with pancreatic cancer undergoing FOLFIRINOX therapy and UGT1A1 genetic polymorphisms.

In conclusion, patients with heterozygous UGT1A1 polymorphisms treated with the original FOLFIRINOX regimen tended to experience severe toxicity more frequently than patients with WT UGT1A1. For patients with heterozygous UGT1A1 polymorphisms, careful management of hematological and gastrointestinal toxicity should be required, and the modified FOLFIRINOX regimen might be appropriate.
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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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