Risk factors for febrile neutropenia in patients with unresectable pancreatic cancer receiving FOLFIRINOX as the first-line treatment.

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Background

・Pancreatic adenocarcinoma was the fourth leading cause of death from cancer in 2013[1], and it carries a poor prognosis: the 5-year survival rate is 7% in Japan.

・In a phase II/III study in 2011, Conroy et al. showed a significant improvement in overall survival with FOLFIRINOX (oxaliplatin, irinotecan, 5-FU, and leucovorin) compared to gemcitabine in patients with metastatic pancreatic cancer[2]. Since then, FOLFIRINOX has become the standard treatment for patients with unresectable pancreatic cancer (URPC) with a good performance status.

・However, FOLFIRINOX can be associated with significant toxicity. A high incidence of febrile neutropenia (FN) (22%) was reported from a Japanese phase II trial of FOLFIRINOX[3].

・The aim of this study was to clarify the risk factors for FN in these patients.

Methods

・A retrospective analysis was performed of the data of patients treated with FOLFIRINOX for histologically proven URPC between July 2011 and January 2015 at the National Cancer Center Hospital, Japan.

・Patients who had received prior chemotherapy or radiation therapy, or who had the UGT genetic polymorphisms of homozygous UGT1A1*6 or UGT1A1*28 or heterozygous UGT1A1*6 and *28 were excluded.

・The demographic and baseline characteristics were compared between patients with FN and without FN by Fisher's exact test for categorical variables or Mann-Whitney's U test for continuous variables.

・The logistic regression model was used to estimate odds ratios (ORs) of the potential risk factors for the development of FN.

Results

Figure. Flow diagram of patient selection.

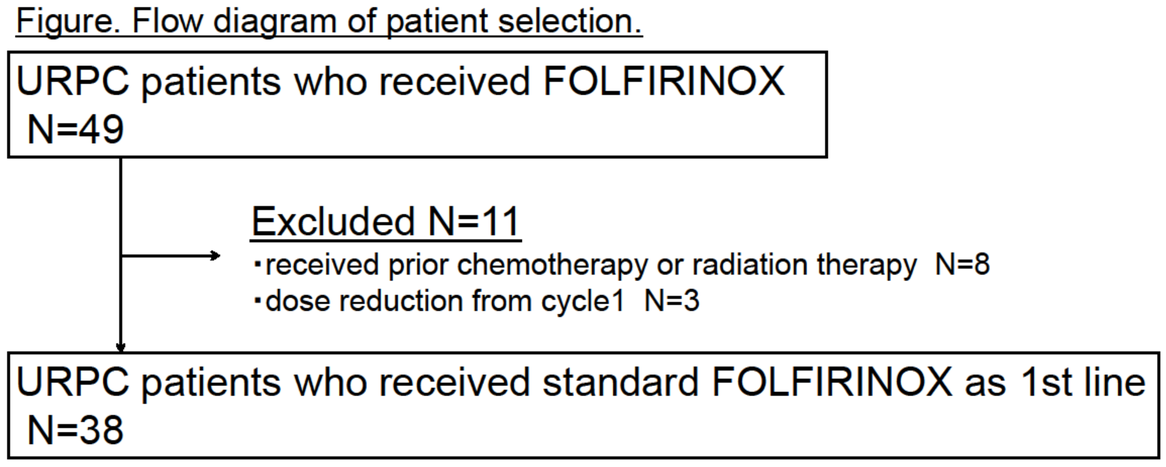

Table1. Characteristics of the patients at baseline.

		N=38	FN group N=9	non-FN group N=29	*P* value
Sex	Male	26	6	20	1.00#
	Female	12	3	9	
Age	Median	60.5	59	61	0.54
	range	22-72	22-66	28-72	
ECOG performance status(PS)	0	16	5	11	0.45#
	1	22	4	18	
UICC-stage	III	12	4	8	0.42#
	IV	26	5	21	
Biliary drainage	No	28	6	22	0.67#
	Yes	10	3	7	
Tumor location	Head	16	4	12	1.00#
	Body or tail	22	5	17	
UGT1A1 polymorphism	Wild type	26	3	23	0.016#
	*6 or *28 hetero	12	6	6	
Body surface area(BSA) (m^2)	Median	1.63	1.63	1.63	0.49
	range	1.35-1.88	1.35-1.87	1.40-1.88	
White blood cell (/μL)	Median	5900	4600	6600	0.037
	range	3700-10080	3900-7100	3700-10080	
Neutrophil (/μL)	Median	3895	3120	4250	0.06
	range	1620-8280	2850-4760	1620-8280	
Lymphocyte (/μL)	Median	1355	1010	1370	0.012
	range	620-2460	620-1890	860-2460	
Monocyte (/μL)	Median	325	290	330	0.23
	range	140-830	140-490	170-830	
Hemoglobin (g/dL)	Median	12.8	12.5	12.9	0.16
	range	8.6-16.6	8.6-13.2	8.9-16.6	
Platelet ($\times 10^4$/μL)	Median	22.25	18.4	23.3	0.11
	range	10.6-40.9	10.6-40.9	12.8-36.2	
Albumin (g/dL)	Median	4.0	4.0	4.0	0.25
	range	3.1-4.7	3.2-4.1	3.1-4.7	
AST (U/L)	Median	20	20	21	0.65
	range	10-86	14-31	10-86	
ALT (U/L)	Median	22.5	18	24	0.72
	range	7-131	8-57	7-131	
Total bilirubin (mg/dL)	Median	0.6	0.6	0.6	0.69
	range	0.3-1.4	0.3-0.8	0.4-1.4	
ALP (U/L)	Median	278.5	276	286	0.59
	range	107-1307	107-725	147-1307	
Creatinine (mg/dL)	Median	0.72	0.77	0.69	0.57
	range	0.45-1.2	0.45-1.2	0.47-1.1	
CRP (mg/dL)	Median	0.34	0.17	0.36	0.98
	range	0.02-7.49	0.02-1.79	0.02-7.49	
CEA (ng/ml)	Median	3.95	4	3.9	0.49
	range	0.8-806	0.8-7.5	1.1-806	
CA19-9 (U/ml)	Median	541.5	164	588	0.46
	range	0-71100	0-4708	0-71100	

#Fisher's exact test ; otherwise Mann-Whitney's U test

Table2. Univariate and multivariate logistic regression analysis for development of FN.

		Univariate analysis			Multivariate analysis		
		OR	95% C.I.	*P* value	OR	95% C.I.	*P* value
Sex	Male	1.00					
	Female	1.11	0.23-5.47	0.89			
Age	＜65	1.00					
	≧65	0.54	0.09-3.12	0.49			
ECOG PS	0	1.00					
	1	049	0.11-2.22	0.35			
UICC-stgae	III	1.00					
	IV	0.48	0.10-2.24	0.35			
Biliary drainage	No	1.00					
	Yes	1.57	0.31-7.99	0.59			
Tumor location	Head	1.00					
	Body or tail	1.13	0.25-5.12	0.87			
UGT1A1 polymorphism	Wild type	1.00			1.00		
	*6 or *28hetero	7.67	1.47-40.0	0.015	8.60	1.36-54.2	0.02
BSA (m^2)	≧1.6	1.00					
	＜1.6	0.99	0.22-4.43	0.98			
White blood cell (/μL)	≧6000	1.00					
	＜6000	4.96	0.87-28.2	0.07			
Neutrophil (/μL)	≧3000	1.00					
	＜3000	5.00	0.93-27.0	0.61			
Lymphocyte (/μL)	≧1500	1.00					
	＜1500	5.65	0.62-51.3	0.12			
Monocyte (/μL)	≧300	1.00					
	＜300	3.28	0.69-15.4	0.13			
Platelet ($\times 10^4$/μL)	≧15	1.00			1.00		
	＜15	6.93	1.17-41.0	0.03	8.07	1.03-63.2	0.047
Albumin (g/dL)	≧4.0	1.00					
	＜4.0	0.86	0.19-3.85	0.84			
Creatinine (mg/dL)	＜1.0	1.00					
	≧1.0	1.08	0.10-11.9	0.95			

Summary

・FN occurred 23.6% (9/38) in the patients with URPC received FOLFIRINOX as first line.

・Univariate and multivariate analysis revealed that significant factors associated with development of FN were presence of heterozygous UGT1A1*6 or *28 and pretreatment platelet count ＜15×10^4 /μL.

Conclusion

・Presence of heterozygous UGT1A1*6 or *28 and pretreatment platelet count ＜15×10^4 /μL might be risk factors for the development of FN in URPC patients receiving FOLFIRINOX.

・The predictive factors proposed in our study could be utilized to select URPC patients at a high risk for the development of FN who may benefit from dose reduction or G-CSF prophylaxis.

・ These findings need clarification with further clinical trials.

References

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