Single center risk factor analysis for febrile neutropenia in pancreatic cancer patients receiving FOLFIRINOX

Ji Young Keum[1], Hee Seung Lee[1], Jung Hyun Jo[1], Moon Jae Chung[1], Jeong Youp Park[1], Seung Woo Park[1], Si Young Song[1] and Seungmin Bang[1]

[1]Division of Gastroenterology, Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea

Disclosures

I have no actual or potential conflict of interest in relation to this work.

Introduction

- Among patients with advanced pancreatic cancer(PC), combination with flurouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) has been one of the first-line options.

- However, a higher incidence of febrile neutropenia (FN) was associated with the FOLFIRINOX regimen.

- Previously, our group published ‘Risk factors for the Occurrence of FN in patients treated with FOLFIRINOX for PC at Cancer chemotherapy and pharmacology. However, this study could not include *UGT1A1* polymorphism.

- We undertook this study for confirming risk factors of FN especially including *UGT1A1* polymorphism in PC patients receiving FOLFIRINOX.

Methods

- We retrospectively collected data of 115 patients with newly diagnosed pancreatic cancer who were planned to treat with first-line FOLFIRINOX between 2017 and 2019 using Pancreatic Cancer Cohort Registry of Severance hospital, Seoul, Korea.

- Patients with homozygous (*6/*6, *28/*28), compound heterozygous (*6/*28), and other type (*1/*73) of *UGT1A1* were excluded for analysis. Also, patients who received reduction dose of FOLFIRINOX and prophylactic G-CSF were excluded.

Results

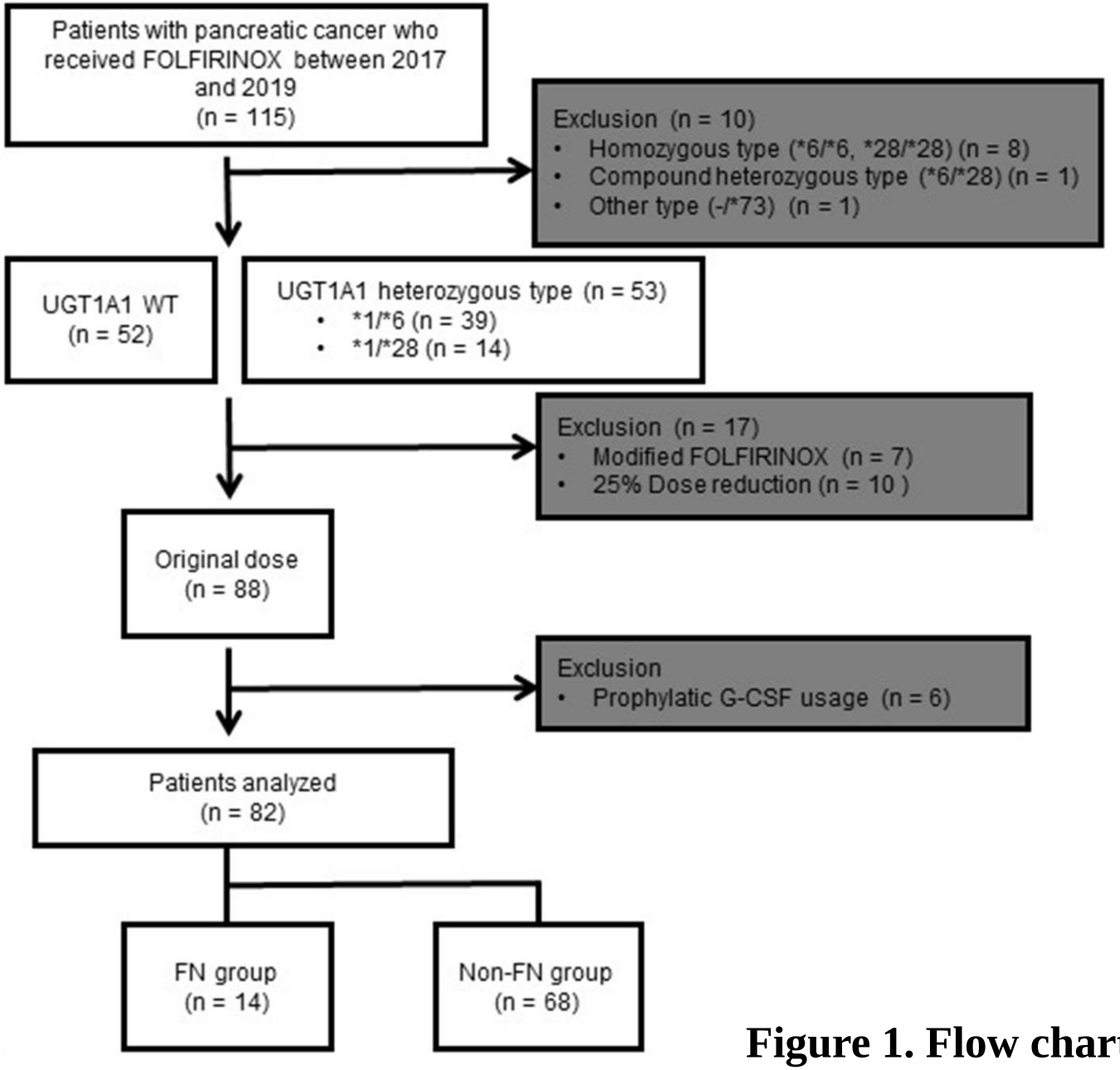

Figure 1. Flow chart of patient selection

Table 1. Baseline characteristics

Variables	All patients (n = 82)	FN group (n = 14)	Non-FN group (n = 68)	*P* value
Patient characteristics				
Age, yr, median	61.5 (38-76)	63.5 (59-76)	60 (38-76)	**0.012**
Sex				
Male	53 (64.6)	6 (42.9)	47 (69.1)	0.073
Female	29 (35.4)	8 (57.1)	21 (30.9)	
ECOG PS				
0	67 (81.7)	11 (78.6)	56 (82.4)	0.714
1	15 (18.3)	3 (21.4)	12 (17.6)	
BMI	23.0 ± 2.8	24.6 ± 3.3	22.6 ± 2.5	**0.015**
DM	29 (35.4)	5 (35.7)	24 (35.3)	1.000
Tumor characteristics				
Location				
Head	46 (56.1)	11 (78.6)	35 (51.5)	0.063
Body/Tail	36 (43.9)	3 (21.4)	33 (48.5)	
Stage				
Resectable	6 (7.3)	1 (7.1)	5 (7.4)	0.835
Borderline Resectable	12 (14.6)	1 (7.1)	11 (16.2)	
Locally advanced	31 (37.8)	5 (35.7)	26 (38.2)	
Metastatic	33 (40.2)	7 (50.0)	26 (38.2)	

Table 1. Baseline characteristics (continued)

Variables	All patients (n = 82)	FN group (n = 14)	Non-FN group (n = 68)	*P* value
UGT1A1				
Wild type	41 (50.0)	3 (21.4)	38 (55.9)	**0.019**
Heterozygous type	41 (50.0)	11 (78.6)	30 (44.1)	
Laboratory characteristics				
WBC, /μL	6755.0 (2550.0-20300.0)	7271.4 (3320.0-11850.0)	6944.1 (2550.0-20300.0)	0.427
Neutrophil, /μL	4000.0 (1070.0-14810.0)	5084.3 (1920.0-9410.0)	4407.8 (1070.0-14810.0)	0.225
Lymphocyte, /μL	1605.0 (550.0-3890.0)	1469.3 (870.0-2080.0)	1680.1 (550.0-3890.0)	0.355
NLR	2.4 (1.0-15.0)	3.7 (1.5-9.2)	2.9 (1.0-15.0)	0.130
Hemoglobin, g/dL	12.2 (9.3-14.6)	12.4 (10.6-14.4)	12.2 (9.3-14.6)	0.767
Platelet, 10^3/μL	225.5 (99.0-695.0)	317.7 (161.0-695.0)	243.5 (99.0-489.0)	**0.045**
Total bilirubin, mg/dL	0.6 (0.3-4.7)	1.0 (0.4-2.4)	0.9 (0.3-4.7)	0.070
AST, IU/L	20.0 (10.0-277.0)	38.1 (12.0-106.0)	33.2 (10.0-277.0)	0.189
ALT, IU/L	22.0 (7.0-635.0)	50.0 (12.0-150.0)	43.4 (7.0-635.0)	**0.038**
CA 19-9, U/mL	183.5 (2.0-20000.0)	4144.2 (3.2-20000.0)	1672.9 (2.0-20000.0)	0.073
Albumin, g/dL	4.0 (3.0-4.8)	3.8 (3.3-4.3)	4.0 (3.0-4.8)	0.178
Initial biliary stent insertion				
No	56 (68.3)	7 (50.0)	49 (72.1)	0.124
Yes	26 (31.7)	7 (50.0)	19 (27.9)	

Mean ± SD, n (%), or median (range)

Table 2. Univariate and multivariate analysis related to febrile neutropenia

Variables		During the entire cycles			
		Univariate		Multivariate	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, yr					
≥ 60		**12.26 (1.52-98.98)**	**0.019**	**22.40 (1.92-261.24)**	**0.013**
Sex					
Male		1.0		1.0	
Female		2.98 (0.92-9.68)	0.069	**11.86 (1.35-104.44)**	**0.026**
BMI					
≥ 25		**3.89 (1.12-13.43)**	**0.032**	**8.97 (1.10-73.17)**	**0.041**
Tumor location					
Body/Tail		1.0	0.070	1.0	**0.034**
Head		3.46 (0.89-13.50)		**10.02 (1.19-84.60)**	
NLR	<3	1.0	0.069	1.0	**0.006**
	≥3	2.98 (0.92-9.68)		**24.51 (2.50-240.56)**	
CA 19-9, U/mL	<100	1.0	0.089		
	≥100	3.26 (0.83-12.73)			
UGT1A1 polymorhpism					
wild type		1.0	**0.027**	1.0	0.094
heterozygous type(-/*6, -/*28)		**4.64 (1.19-18.16)**		4.34 (0.78-24.11)	

- The multivariate logistic regression analysis showed that age ≥ 60 (OR, 22.40; P = 0.013), female sex (OR, 11.86; P = 0.026), BMI ≥ 25 (OR, 8.97; P=0.041), Tumor location: Head (OR, 10.02, P = 0.034) and NLR ≥ 3 (OR, 24.51; P = 0.006) were significantly related to a high risk of FN.
- Time-dependent bias was reduced using Cox regression analysis, which revealed that age ≥ 60 (OR, 13.22; *P* = 0.013), NLR ≥ 3 (OR, 3.01; *P* = 0.042), and *UGT1A1* heterozygous type (OR, 4.70; *P* = 0.018) were significant risk factors.
- In *UGT1A1* heterozygous type group, most patients experienced FN within cycle 4, which is early phase of chemotherapy.

Table 3. Multivariate analysis with the Cox proportional hazards model to febrile neutropenia

Variables	Febrile neutropenia				
	Unadjusted OR	*P* value	Adjusted OR	95% CI	*P* value
Age, yr ≥ 60	11.05	0.021	**13.22**	1.73-101.30	**0.013**
NLR ≥ 3	2.56	0.082	**3.01**	1.04-8.71	**0.042**
UGT1A1 heterozygous type	3.91	0.037	**4.70**	1.31-16.90	**0.018**

Conclusion

- Age ≥ 60, NLR ≥ 3, and *UGT1A1* heterozygous type were independent risk factors for the development of FN in patients with pancreatic cancer treated with FOLFIRINOX.
- Considering *UGT1A1* polymorphism is risk factor for early phase FN development in pancreatic cancer patient receiving FOLFIRINOX, it is thought that UGT1A1 test will be needed to prevent FN when starting FOLFIRINOX.