의학박사 학위논문

The effect of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in patients with metastatic pancreatic cancer on high expression of human equilibrative nucleoside transporter 1

울산대학교 대학원

의학과

권재우

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지도교수 : 황 대 욱

이 논문을 박사 학위 논문으로 제출함

2023년 8월

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권재우의 박사학위 논문을 인준함.

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목차

국문요약

전이성 췌장암 환자에서 높은 hENT1 발현정도에 따른 Nab-paclitaxel plus gemcitabine 과 FOLFIRINOX 의 효과 비교

서론 : 진행성 췌장암에 대한 표준 1차 항암화학 요법은 nab-paclitaxel and gemcitabine (AG) 요법과 and 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX)요법 입니다. 그러나, gemcitabine의 흡수를 촉진하는 수송체인 hENT1의 발현이 강한 환자군에게 두 항암 요법의 효과를 비교하는 연구는 아직 부족한 실정입니다. 따라서 본 연구의 목적은 hENT1 발현에 따른 전이성 췌장암 환자에서 AG 요법과 FOLFIRINOX 요법의 효과를 비교하는 것이었습니다.

연구 대상 및 방법 : 2013년부터 2016년까지 대규모 단일 기관에서 AG 또는 FOLFIRINOX로 치료한 전이성 췌장암 환자 153명을 후향적으로 분석했습니다. 환자들은 hENT1 발현과 1차 항암 요법에 따라하여 분류하였습니다. 각 환자군의

전체생존기간 및 암이 진행하지 않는 생존기간을 비교했습니다. 예후위험인자를 확인 후 위험인자의 조건에 따라 하위그룹 간의 추가 비교를 시행하였습니다.

결과 : 인구통계학적으로 hENT1발현이 강한 환자군은 hENT1발현이 약한 환자군보다 간 전이의 비율이 높았으며 (76.6% vs. 56.2%, p=0.007), 폐 전이는 낮은 비율(12.5% vs. 16.9%, p=0.043)을 보였습니다. 전체생존기간의 중앙값은 hENT1발현이 약하면서 FOLFIRINOX 치료를 받은 환자군보다 hENT1 발현이 강하면서 AG치료를 받은 환자군에서 더 우수했습니다(10.3개월 vs. 15.4개월, p = 0.005). 예후 위험인자로 ECOG2와 간 전이가 확인되었으며, AG치료를 받은 ECOG0 또는 1 이면서 간 전이 가 있는 환자를 대상으로 한 하위그룹 분석 결과 hENT1 발현이 강한 환자군이 hENT1 발현이 약한 환자군 보다 전체생존기간 중간값이 더 우월하였습니다 (15.7개월 vs. 10.8 개월, p = 0.021). 또한 FOLFIRINOX로 치료 받은 환자군에 비해서도 더 나은 생존기간을 보였습니다. (15.7개월 vs. 9.3개월, p = 0.040).

결론 : AG 항암요법은 hENT1 발현이 강한 전이성 췌장암 환자에게 효과적인 항암요법 입니다. 특히 ECOG 0 또는 1 이면서 간 전이가 있는 전이성 췌장암환자에게 hENT1 발현이 강할 경우 AG 요법은 1차 항암요법으로 고려되어야 합니다.

Table 1. Baseline patient characteristics according to chemotherapy regimen

Variables		AG (n=78)	FOLFIRINOX (n=75)	*P* value
Age, years, (±SD)	Mean	60.23 (±9.5)	58.8 (±9.6)	0.379
	<65	52 (66.7%)	52 (69.3%)	
	≥65	26 (33.3%)	23 (30.7%)	
Sex, n, (%)	Female	34 (43.6%)	21 (28.0%)	0.033
	Male	44 (56.4%)	54 (72.0%)	
Biopsy method, n, (%)	Excision	22 (28.2%)	17 (22.7%)	0.274
	FNA	56 (71.8%)	58 (77.3%)	
Biopsy location, n, (%)	Pancreas	44 (56.4%)	43 (57.3%)	>0.999
	Other	34 (43.6%)	32 (42.7%)	
ECOG PS, n, (%)	0 or 1	75 (96.2%)	75 (100%)	0.130
	2	3 (3.8%)	0 (0.0%)	
Primary tumor site, n, (%)	Head	25 (32.1%)	33 (44.0%)	0.156
	Body	15 (19.2%)	10 (13.3%)	
	Tail	20 (25.6%)	23 (30.7%)	
	Multicentric	18 (23.1%)	9 (12.0%)	
Site of metastasis, n, (%)	Liver	48 (61.5%)	51 (68.0%)	0.253
	Peritoneum	28 (35.9%)	18 (24.0%)	0.076
	Lung	16 (20.5%)	7 (9.3%)	0.043
	Bone	4 (5.1%)	2 (2.7%)	0.359
	Lymph node	35 (44.9%)	17 (22.7%)	0.003
Number of involved metastatic sites, n, (%)	<2	37 (47.4%)	55 (73.3%)	0.001
	≥2	41 (52.6%)	20 (26.7%)	

CA 19-9, n, (%)	Normal	17 (22.1%)	13 (17.3%)	0.758
	> UNL	60 (77.9%)	62 (82.7%)	
Histoscore, n, (%)	≤3 (no/weak hENT1)	46 (59.0%)	43 (57.3%)	0.298
	> 3 (strong hENT1)	32 (41.0%)	32 (42.7%)	
	0	4 (5.1%)	5 (6.7%)	
	1	17 (21.8%)	13 (17.3%)	
	2	15 (19.2%)	15 (20.0%)	
	3	10 (12.8%)	10 (13.3%)	
	4	12 (15.4%)	16 (21.3%)	
	6	12 (15.4%)	8 (10.7%)	
	8	2 (2.6%)	2 (2.7%)	
	9	4 (5.1%)	3 (4.0%)	
	12	2 (2.6%)	3 (4.0%)	
Second-line	Yes	45 (59.2%)	62 (82.7%)	< 0.001
chemotherapy, n, (%)	Fluoropyrimidine	42 (93.3%)	2 (3.2%)	
	Gemcitabine	1 (2.2%)	60 (96.8%)	
	Other	2 (4.4%)	0 (0.0%)	
	No	31 (40.8%)	13 (17.3%)	

AG, nab-paclitaxel and gemcitabine; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; SD, standard deviation; FNA, fine needle aspiration; ECOG PS, Eastern Cooperative Oncology Group performance status; UNL, upper normal limit

Table 2. Baseline patient characteristic according to hENT1 expression

Variables		Strong hENT1 (n=64)	No/weak hENT1 (n=89)	*P* value
Age, years, (±SD)	Mean	58.4 (±9.9)	60.40 (±9.3)	0.199
	<65	46 (71.9%)	58 (65.2%)	
	≥65	18 (28.1%)	31 (34.8%)	
Sex, n, (%)	Female	18 (28.1%)	37 (41.6%)	0.061
	Male	46 (71.9%)	52 (58.4%)	
Biopsy method, n, (%)	Excision	20 (31.3%)	19 (21.3%)	0.116
	FNA	44 (68.8%)	70 (78.7%)	
Biopsy location, n, (%)	Pancreas	31 (48.4%)	56 (62.9%)	0.098
	Other	33 (51.6%)	33 (37.1%)	
ECOG PS, n, (%)	0 or 1	63 (98.4%)	87 (97.8%)	0.622
	2	1 (1.6%)	2 (2.2%)	
Primary tumor site, n, (%)	Head	23 (35.9%)	35 (39.3%)	0.662
	Body	9 (14.1%)	16 (18.0%)	
	Tail	18 (28.1%)	25 (28.1%)	
	Multicentric	14 (21.9%)	13 (14.6%)	
Site of metastasis, n, (%)	Liver	49 (76.6%)	50 (56.2%)	0.007
	Peritoneum	14 (21.9%)	32 (36.0%)	0.074
	Lung	8 (12.5%)	15 (16.9%)	0.043
	Bone	1 (1.6%)	5 (5.6%)	0.402
	Lymph node	21 (32.8%)	31 (34.8%)	0.863
Number of involved metastatic sites, n, (%)	<2	40 (62.5%)	52 (58.4%)	0.621
	≥2	24 (37.5%)	37 (41.6%)	
CA 19-9, n, (%)	Normal	13 (20.3%)	17 (19.3%)	>0.999
	> UNL	51 (79.7%)	71 (80.7%)	

Chemotherapy regimen, n, (%)	AG	32 (50.0%)	46 (51.7%)	0.483
	FOLFIRINOX	32 (50.0%)	43 (48.3%)	
Second-line chemotherapy, n, (%)	Yes	46 (73.0%)	61 (69.3%)	0.089
	Fluoropyrimidine	15 (32.6%)	29 (47.5%)	
	Gemcitabine	29 (63.0%)	32 (52.5%)	
	Other	2 (4.3%)	0 (0.0%)	
	No	17 (27.0%)	27 (30.7%)	

SD, standard deviation; FNA, fine needle aspiration; ECOG PS, Eastern Cooperative Oncology Group performance status; UNL, upper normal limit; AG, nab-paclitaxel and gemcitabine; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin

Table 3. Baseline patient characteristics according to hENT1 expression

Variables		AG & strong hENT1 n=32	AG & no/weak hENT1 n=46	FOLFIRINOX & strong hENT1 n=32	FOLFIRINOX & no/weak hENT1 n=43
Age, years, (±SD)	Mean	59.3 (±9.4)	60.9 (±9.6)	57.5 (±10.4)	59.9 (±9.0)
	<65	23 (71.9%)	29 (63.0%)	23 (71.9%)	29 (67.4%)
	≥65	9 (28.1%)	17 (27.0%)	9 (28.1%)	14 (32.6%)
	P value*	reference	0.768	0.491	0.776
Sex, n, (%)	Female	12 (37.5%)	22 (47.8%)	6 (18.8%)	15 (34.9%)
	Male	20 (62.5%)	24 (52.2%)	26 (81.3%)	28 (65.1%)
	P value*	reference	0.251	0.082	>0.999
Biopsy method, n, (%)	Excision	12 (37.5%)	10 (21.7%)	8 (25.0%)	9 (20.9%)
	FNA	20 (62.5%)	36 (78.3%)	24 (75.0%)	34 (79.1%)
	P value*	reference	0.103	0.209	0.094
Biopsy location, n, (%)	Pancreas	14 (43.8%)	30 (65.2%)	17 (53.1%)	26 (60.5%)
	Other	18 (56.3%)	16 (34.8%)	15 (46.9%)	17 (39.5%)
	P value*	reference	0.068	0.617	0.168
ECOG PS, n, (%)	0 or 1	31 (96.9%)	44 (95.7%)	32 (100.0%)	43 (100.0%)
	2	1 (3.1%)	2 (4.3%)	0 (0.0%)	0 (0.0%)
	P value*	reference	0.635	0.500	0.427
Primary tumor site, n, (%)	Head	10 (31.3%)	15 (32.6%)	13 (40.6%)	20 (46.5%)
	Body	7 (21.9%)	8 (17.4%)	2 (6.3%)	8 (18.6%)
	Tail	6 (18.8%)	14 (30.4%)	12 (37.5%)	11 (25.6%)
	Multicentric	9 (28.1%)	9 (19.6%)	5 (15.6%)	4 (9.3%)
	P value*	reference	0.622	0.106	0.158
Site of metastasis,	Liver	27 (84.4%)	21 (45.7%)	22 (68.8%)	29 (67.4%)
	P value*	reference	0.001	0.237	0.114

n, (%)	Peritoneum	8 (25.0%)	20 (43.5%)	6 (18.8%)	12 (27.9%)
	P value*	reference	0.149	0.763	0.799
	Lung	3 (9.4%)	13 (28.3%)	5 (15.6%)	2 (4.7%)
	P value*	reference	0.037	0.354	0.645
	Bone	0 (0.0%)	4 (8.7%)	1 (3.1%)	1 (2.3%)
	P value*	reference	0.140	>0.999	>0.999
	Lymph node	13 (40.6%)	22 (47.8%)	8 (25.0%)	9 (20.9%)
	P value*	reference	0.645	0.287	0.077
Number of involved metastatic sites, n, (%)	<2	18 (56.3%)	19 (41.3%)	22 (68.8%)	33 (76.7%)
	≥2	14 (43.8%)	27 (58.7%)	10 (31.3%)	10 (23.3%)
	P value*	reference	0.142	0.439	0.081
CA 19-9, n, (%)	Normal	9 (28.1%)	8 (17.8%)	4 (12.5%)	9 (20.9%)
	> UNL	23 (71.9%)	37 (82.2%)	28 (87.5%)	34 (79.1%)
	P value*	reference	0.211	0.213	0.587
Second-line chemotherapy, n, (%)	Yes	17 (54.8%)	28 (62.2%)	29 (90.6%)	33 (76.7%)
	Fluoropyrimidine	14 (82.4%)	28 (100.0%)	1 (3.4%)	1 (3.0%)
	Gemcitabine	1 (5.9%)	0 (0.0%)	28 (96.6%)	32 (97.0%)
	Other	2 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	14 (45.2%)	17 (37.8%)	3 (9.4%)	10 (23.3%)
	P value*	reference	0.048	<0.001	<0.001

SD, standard deviation; FNA, fine needle aspiration; ECOG PS, Eastern Cooperative Oncology Group performance status; UNL, upper normal limit; AG, nab-paclitaxel and gemcitabine; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin

* *P* value: vs. AG & hENT1 strong group

Table 4. Objective response according to regimen and hENT1 expression

Variables		AG & strong hENT1 n=32	AG & no/weak hENT1 n=46	FOLFIRINOX & strong hENT1 n=32	FOLFIRINOX & no/weak hENT1 n=43
Best response	CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	PR	12 (37.5%)	11 (23.9%)	14 (43.8%)	11 (26.2%)
	SD	8 (25.0%)	20 (43.5%)	9 (28.1%)	16 (38.1%)
	PD	6 (18.8%)	6 (13.0%)	8 (25.0%)	12 (28.6%)
	NA	6 (18.8%)	9 (19.6%)	1 (3.1%)	3 (7.1%)
	P value*	reference	0.340	0.291	0.279
ORR	(CR+PR)	12 (37.5%)	11 (23.9%)	14 (43.8%)	11 (26.2%)
	P value*	reference	0.198	>0.999	0.187
DCR	(CR+PR+SD)	20 (62.5%)	31 (67.4%)	23 (71.9%)	27 (64.3%)
	P value*	reference	0.530	>0.999	0.579

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease;

ORR, overall response rate;

DCR, disease control rate

* *P* value: vs. AG & hENT1 strong group

Table 5. Univariate and multivariate models of risk factors for progression-free survival

Variables	Univariate HR (Lower, upper; 95% CI)	p-value	Multivariate HR (Lower, upper; 95% CI)	p-value
Group (ref = AG & strong)				
AG & no/weak	1.477 (0.925, 2.359)	0.102		
FOLFIRINOX & strong	1.27 (0.759, 2.126)	0.362		
FOLFIRINOX & no/weak	1.788 (1.11, 2.88)	0.017		
Sex				
Female	1.11 (0.792, 1.554)	0.545		
Age (ref = <65)				
>65	1.099 (0.775, 1.558)	0.597		
ECOG (ref = ECOG 0 or 1)				
ECOG 2	3.101 (0.757, 12.701)	0.116	4.832 (1.148, 20.345)	0.032
CA 19-9 (ref = normal)				
>UNL	1.409 (0.94, 2.114)	0.097	1.349 (0.86, 2.116)	0.192
Liver metastasis (ref = none)				
Yes	1.108 (0.785, 1.563)	0.56	1.492 (1.019, 2.183)	0.04
Bone metastasis (ref = none)				
Yes	1.462 (0.596, 3.586)	0.407	2.2 (0.881, 5.497)	0.091
Peritoneum metastasis (ref = none)				
Yes	0.994 (0.695, 1.421)	0.974		
Lung metastasis (ref = none)				
Yes	1.033 (0.659, 1.62)	0.887	1.36 (0.825, 2.243)	0.228
Distant lymph node meta (ref = none)				
Yes	1.215 (0.859, 1.717)	0.271		
Multiple metastasis (ref = none)				
Yes	0.987 (0.707, 1.378)	0.94		
Primary location (ref = none)				
Head	1.061 (0.756, 1.489)	0.731		

HR, hazard ratio; CI, confidence interval; AG, nab-paclitaxel and gemcitabine; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; ECOG, Eastern Cooperative Oncology Group; UNL, upper normal limit

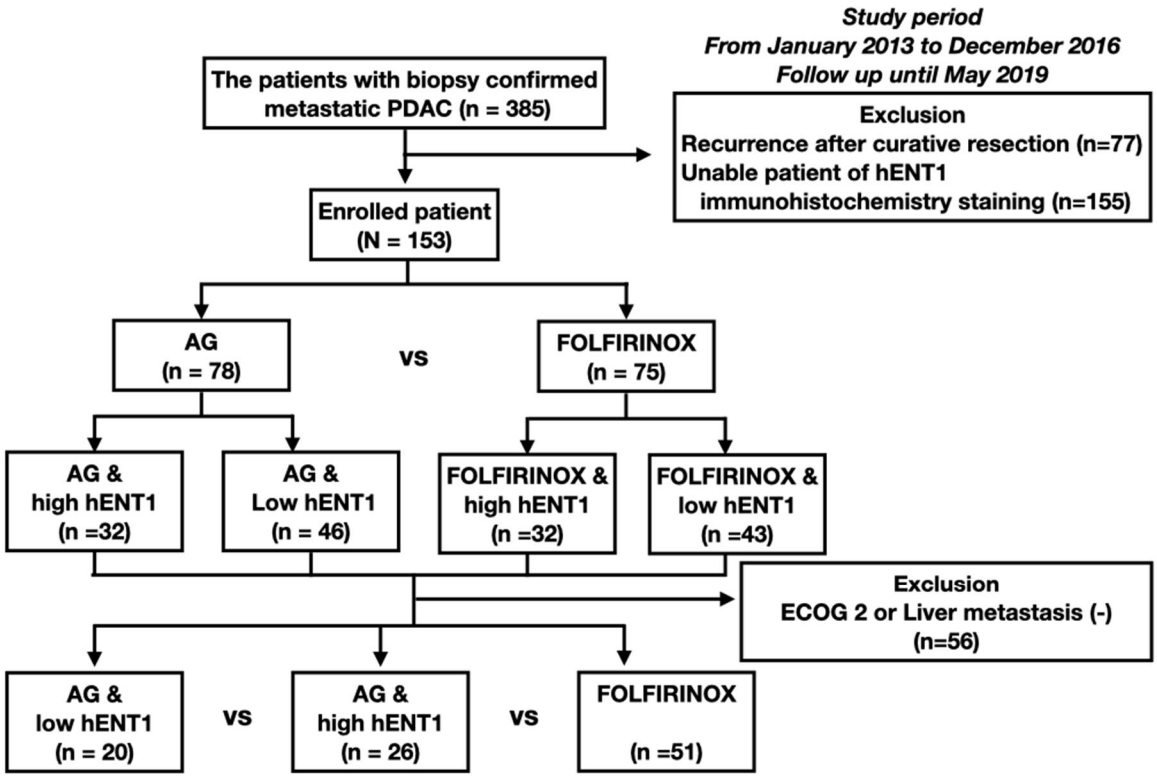

Figure 1. Patient flow diagram. We conducted a retrospective review of 153 patients who underwent first-line AG or FOLFIRINOX after excluding 232 patients based on the criteria listed in the figure. Patients were classified according to expression of hENT1, and the four patient groups were compared (AG & strong hENT1 vs. AG & no/weak hENT1 vs. FOLFIRNOX & strong hENT1 vs. FOLFIRINOX & no/weak hENT1). To further elucidate the effects of hENT1, we performed an analysis in which we stratified patients according to ECOG performance status and liver metastasis, both of which were found to be risk factors for PFS in this study. Subsequently, we compared the survival rates among the patient groups.

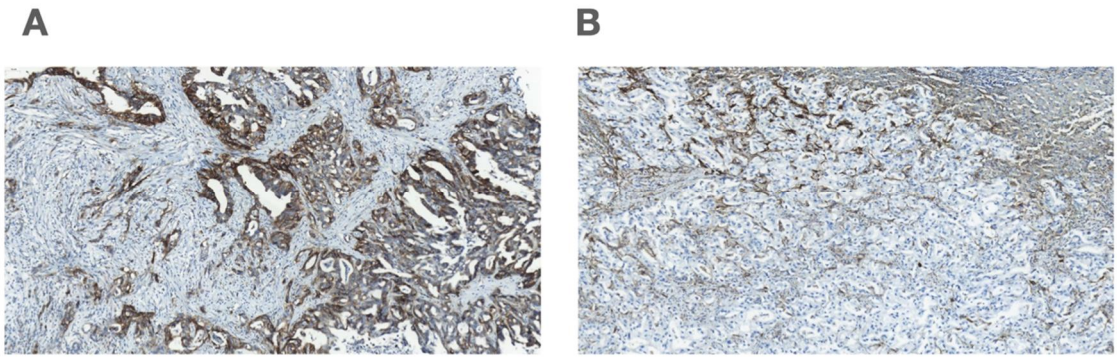

Figure 2. These slides depict histological images from mPC patients. The slides were stained with an anti-human equilibrative nucleoside transporter 1 (hENT1) primary rabbit monoclonal antibody clone named SP120. (A) Strong expression of hENT1. (B) No/weak expression of hENT1.

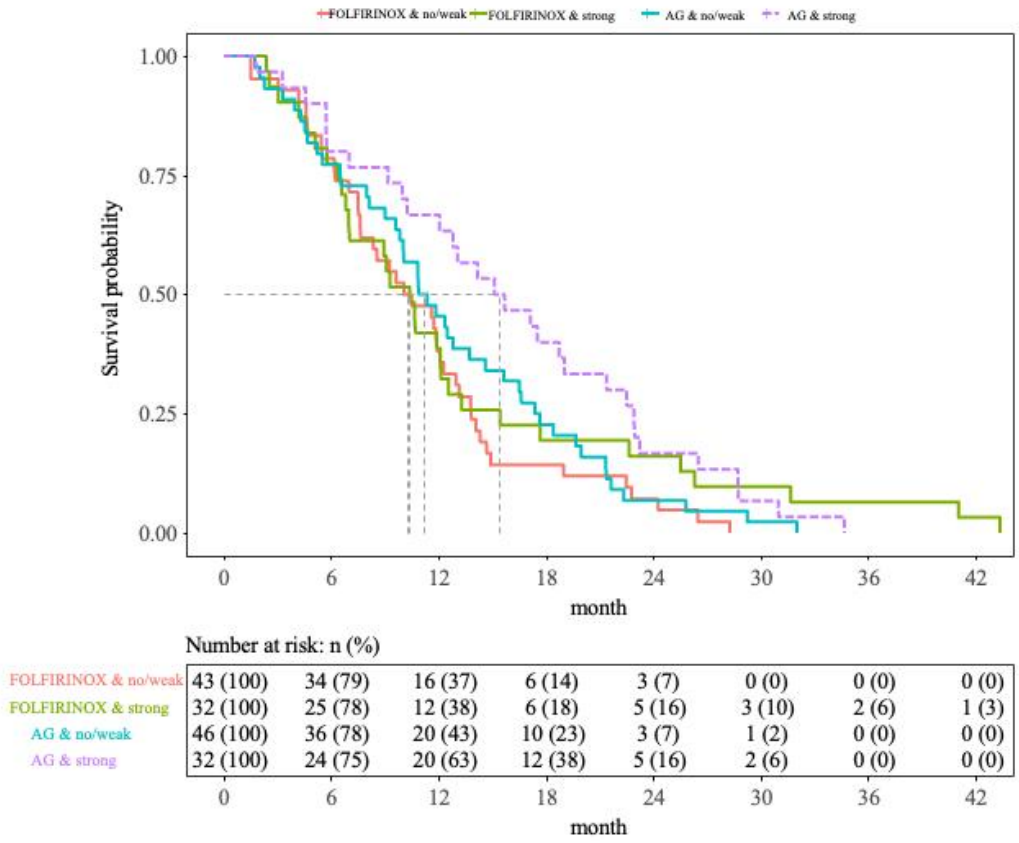

Figure 3. Kaplan-Meier overall survival curves by first-line chemotherapy regimen and hENT1 expression. The median OS was 15.4 months in the AG with strong hENT1 group, 11.1 months in the AG with no/weak hENT1 group, 10.4 months in the FOLFIRINOX with strong hENT1 group, and 10.3 months in the FOLFIRINOX with no/weak hENT1 group. The 1-year OS rate was 63% in the AG with strong hENT1 group, which is better than in the other groups (43% in the AG with no/weak hENT1 group, 38% in the FOLFIRINOX with strong hENT1 group, and 37% in the FOLFIRINOX with no/weak hENT1 group). Although no statistically significant difference was observed between the AG with strong hENT1 group and the AG with no/weak hENT1 group (p=0.06) or the FOLFIRINOX with strong hENT1 group (p=0.4), the difference between the AG with strong hENT1 group and the FOLFIRINOX with no/weak hENT1 group was statistically significant (p =0.005).

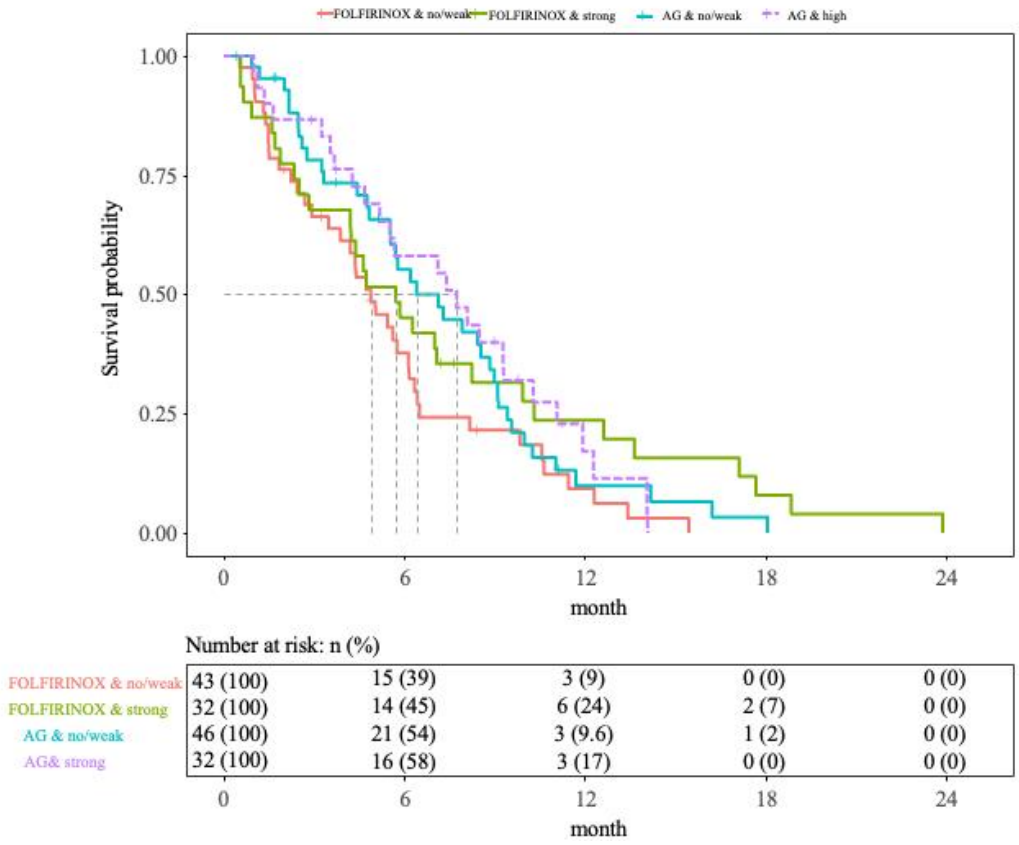

Figure 4. Kaplan-Meier progression-free survival curves by first-line chemotherapy regimen and hENT1 expression. The median PFS was 7.8 months in the AG with strong hENT1 group, 6.4 months in the AG with no/weak hENT1 group, 5.7 months in the FOLFIRINOX with strong hENT1 group, and 4.9 months in the FOLFIRINOX with no/weak hENT1 group. The 1-year PFS rate was 17.1% in the AG with strong hENT1 group, 9.6% in the AG with no/weak hENT1 group, 23.6% in the FOLFIRINOX with strong hENT1 group, and 9.2% in the FOLFIRINOX with no/weak hENT1 group. No statistically significant differences were found between groups (AG with strong hENT1 group vs. AG with no/weak hENT1 group, $p = 0.7$; vs. FOLFIRINOX with strong hENT1 group, $p > 0.999$; vs. FOLFIRINOX with no/weak hENT1 group, $p=0.1$).

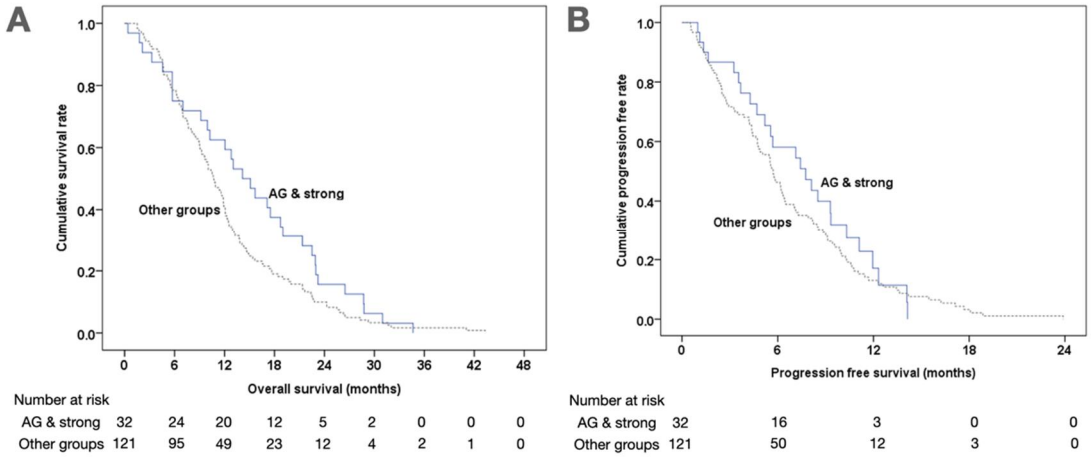

Figure 5. Kaplan-Meier survival curve for patients in the AG with strong hENT1 group compared with those in all other groups. (A) The median OS and 1-year OS rate were 15.4 months and 63%, respectively, in the AG with strong hENT1 group and 10.7 months and 40.5% in the other groups (p = 0.091). (B) The median PFS and 1-year PFS rate were 7.8 months and 17.1%, respectively, in the AG with strong hENT1 group and 5.7 months and 17.1% in the other groups (p = 0.412).

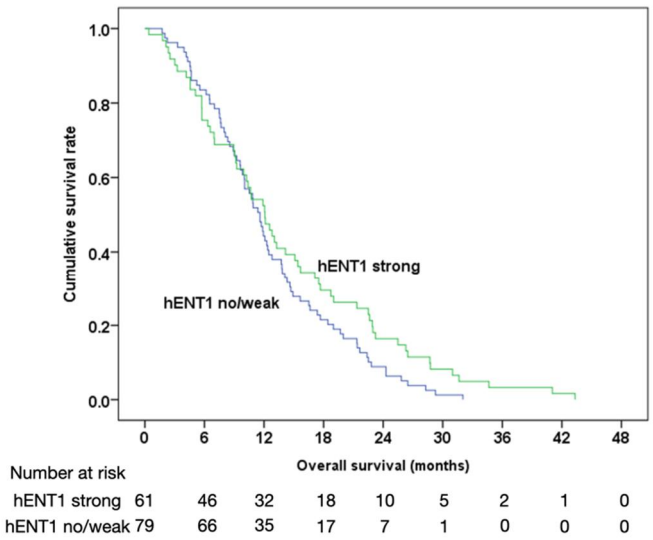

Figure 6. Kaplan-Meier survival curve in patients treated with a gemcitabine regimen (including AG) as first- or second-line chemotherapy. The median OS and 1-year OS were 12.1 months and 52.5%, respectively, in the strong hENT1 group and 11.6 months and 44.3% in the no/weak hENT1 group. No significant differences were found between the groups (p = 0.106).

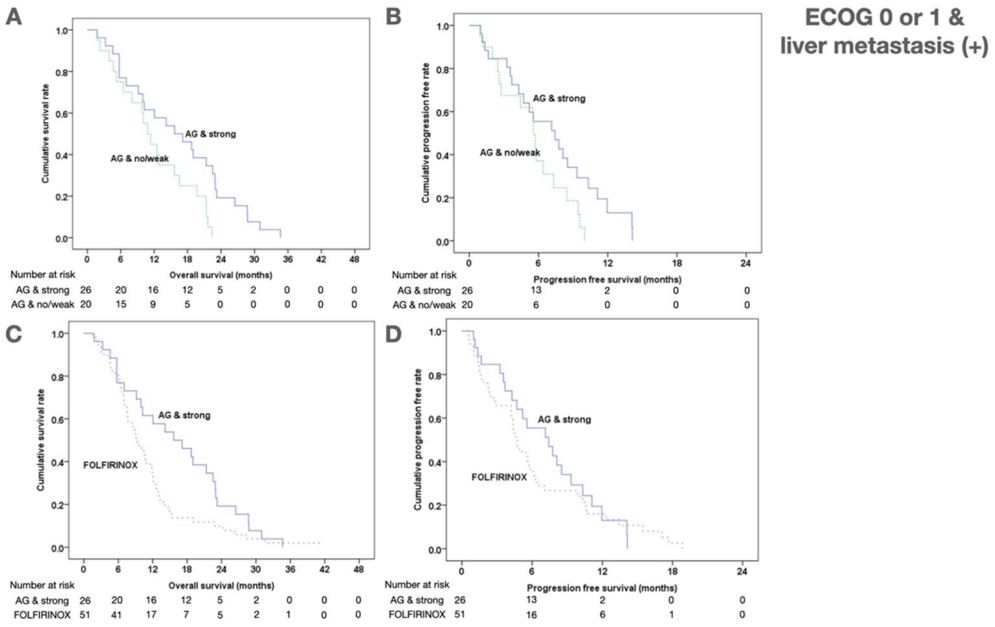

Figure 7. Kaplan-Meier survival curve in patients with ECOG 0 or 1 and liver metastasis. (A) The median OS was 15.7 months in the AG with strong hENT1 group (n=26) and 10.8 months in the AG with no/weak hENT1 group (n=20), $p = 0.021$. (B) The median PFS was 7.4 months in the AG with strong hENT1 group and 5.5 months in the AG with no/weak hENT1 group, $p = 0.081$. (C) The median OS was 15.7 months in the AG with strong hENT1 group (n=26) and 9.3 months in the FOLFIRINOX group (n=51), $p = 0.040$. (D) The median PFS was 7.4 months in the AG with strong hENT1 group and 4.7 months in the FOLFIRINPX group ($p = 0.514$).

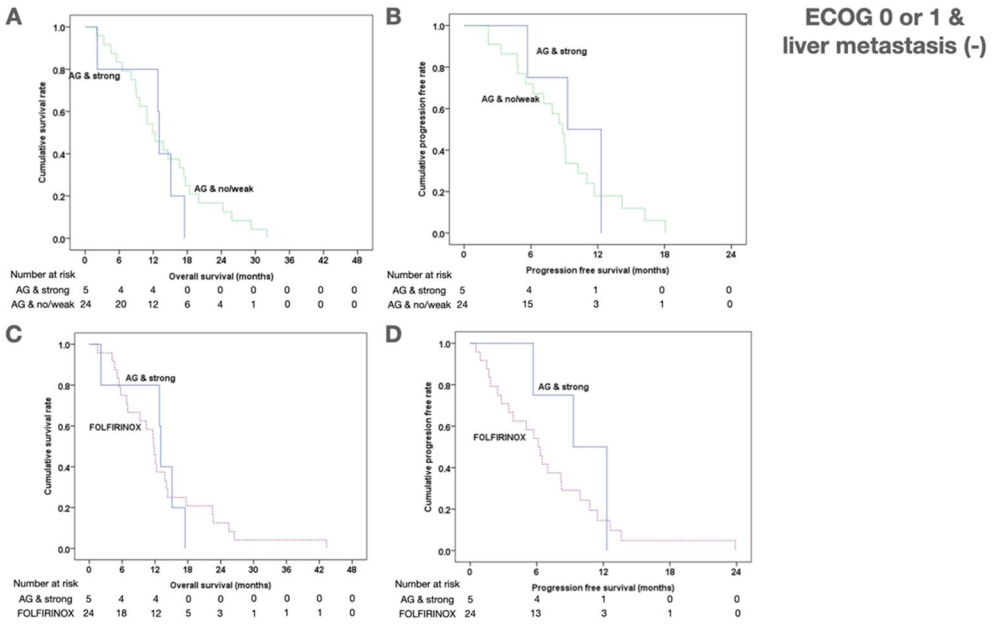

Figure 8. Kaplan-Meier survival curve in patients with ECOG 0 or 1 and without liver metastasis. (A) The median OS was 13.0 months in the AG with strong hENT1 group (n=5) and 11.9 months in the AG with no/weak hENT1 group (n=24), $p = 0.563$. (B) The median PFS was 9.3 months in the AG with strong hENT1 group and 8.8 months in the AG with no/weak hENT1 group, $p = 0.582$. (C) The median OS was 13.0 months in the AG with strong hENT1 group (n=5) and 11.7 months in the FOLFIRINOX group (n=24), $p = 0.897$. (D) The median PFS was 9.3 months in the AG with strong hENT1 group and 6.1 months in the FOLFIRINPX group, $p = 0.381$.

서론(Introduction)

Pancreatic cancer is one of the most aggressive malignancies in the world and the fifth leading cause of cancer-related deaths in Korea[1]. Only 10–20% of cases are potentially curable with surgery upon diagnosis[2, 3], and the 60% of patients who present with stage IV disease are most commonly treated with systemic chemotherapy to enhance survival time and mitigate cancer-related symptoms[4, 5]. The most common first-line chemotherapy regimens for metastatic pancreatic cancer (mPC) are a combination of *nab*-paclitaxel and gemcitabine (AG) and FOLFIRINOX, which comprises 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin[6]. The most effective of these regimens is not yet clear[7, 8]. A recent nonrandomized comparative effectiveness study involving 1102 mPC patients suggested that FOLFIRINOX might be a better treatment option than AG[9]. However, that study also reported that the FOLFIRINOX regimen was administered primarily to patients who are younger, have better performance status, and fewer comorbidities than those treated with AG. In a

randomized clinical trial that compared FOLFIRINOX with gemcitabine for mPC patients, FOLFIRINOX demonstrated superior survival times but was associated with increased toxicity[10]. Therefore, the potential benefits and risks of FOLFIRINOX should be carefully considered when determining an optimal treatment for mPC patients. A recent study conducted at our institution indicated that AG and FOLFIRINOX had comparable efficacy, and that AG might offer potential benefits for patients with peritoneal metastases or severe comorbidities[11]. Given the drug toxicity associated with FOLFIRINOX, AG therapy might be a viable treatment option for older patients with mPC and multiple comorbidities. In addition, clinicians should consider the possibility of conversion surgery when selecting an appropriate neoadjuvant chemotherapy regimen such as FOLFIRNOX or AG, as well as patient performance status and disease entity.

Human equilibrative nucleoside transporter 1 (hENT1), which is encoded by SLC29A1, is a specialized integral membrane transporter for crossing plasma

membranes and a major mediator of gemcitabine uptake into cells[12-14]. In a healthy pancreas, hENT1 has moderate expression in exocrine glandular cells and low expression in the islets of Langerhans; pancreatic tumors, on the other hand, show a decrease in hENT1 expression[15]. Several reports have indicated that strong hENT1 expression is a positive sign in pancreatic cancer patients treated with gemcitabine-based chemotherapy[14, 16, 17]. In addition, it has been reported that nab-paclitaxel, which is an albumin-stabilized paclitaxel formulation that induces angiogenesis and increases the perfusion and delivery of gemcitabine into cells, potentiates gemcitabine activity[18]. In a phase 3 clinical trial for patients with mPC, AG significantly improved the overall survival (OS), progression-free survival (PFS), and response rate compared with gemcitabine alone[19]. Those results suggest that better survival outcomes can be obtained when AG is administered to pancreatic cancer patients with strong hENT1 expression. However, few studies have examined whether survival outcomes differ between pancreatic cancer patients with strong hENT1 expression

treated with AG and those treated with FOLFIRINOX. Recently, Perera S. et al. reported that patients with advanced pancreatic ductal adenocarcinoma who had high hENT1 mRNA expression and were treated with AG demonstrated longer OS than patients with low hENT1 expression[20]. However, there is a paucity of studies that have utilized an anti-hENT1 monoclonal antibody to confirm the effect of AG on hENT1 expression. The purpose of this study is to retrospectively assess the efficacy of AG and FOLFIRINOX in patients with mPC based on hENT1 expression, as shown by anti-hENT1 monoclonal antibody.

연구 방법 (Materials and methods)

Patients

A total of 385 histologically confirmed mPC patients treated with first - line AG or FOLFIRINOX (or modified FOLFIRINOX) from January 2013 to December 2016 at Asan Medical center, were included in this analysis and first study for this cohort have been reported previously in our institution[11]. Patients with recurrence after curative resection (n=77) were excluded from this study because of potential bias from the previous operation.

None of the patients underwent conversion surgery after receiving chemotherapy. We excluded 155 patients due to insufficient tissue volume or status for hENT1 expression staining. Finally, 153 patients eligible for slide review and immunohistochemistry staining with the hENT1 expression antibody were enrolled in the final analysis. The patient flow diagram is presented in Figure 1. Clinical data about those patients were obtained from the electronic medical records of Asan Medical Center and reviewed

retrospectively. The following clinicopathological data were collected and analyzed: sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor site, histology, site of metastasis, CA19-9, treatment duration of first-line chemotherapy, OS, and PFS. OS was measured from the time of chemotherapy initiation until death or the date at which the patient was lost from the national insurance data. Disease progression was diagnosed as identification of new progressive lesions using ^{18}F-fluorodeoxyglucose positron emission tomography, computed tomography, or magnetic resonance imaging and elevated CA 19-9 level. PFS was defined as the duration from initiation of first-line chemotherapy until a diagnosis of progression or death from any cause, whichever occurred first. Written consent from the patients was not required because this study is a retrospective cohort study, and all enrolled patients had died by the time of study planning. This retrospective cohort study was approved by the Institutional Review Board of Asan Medical Center (approval number: 2019-1216).

Treatment and response assessment

The administration methods for AG and FOLFIRNOX were described in our earlier institutional study[11]. AG, which consisted of a 30-minute intravenous infusion of *nab*-paclitaxel at a dose of 125 mg/m^2 followed by gemcitabine at a dose of 1000 mg/m^2, was administered on days 1, 8, and 15 every 4 weeks, as in the MPACT trial[19]. FOLFIRINOX, which consisted of a 2-hour intravenous infusion of oxaliplatin 85 mg/m^2, a 90-minute intravenous infusion of irinotecan 180 mg/m^2, a 2-hour infusion of leucovorin 400 mg/m^2, an intravenous bolus of 5-FU 400 mg/m^2, and a 46-hour continuous infusion of 5-FU 2400 mg/m^2, was administered every 2 weeks, as in the PRODIGE 4 trial[10]. Modified FOLFIRINOX (dose of irinotecan reduced to 150 mg/m^2 and omission of the bolus 5-FU) was used at the physician's discretion. Tumor response was evaluated every 6–8 weeks using computed tomography and was graded according to the Response Evaluation Criteria in Solid Tumors version 1.1[21].

Construction of immunohistochemical staining

Formalin fixed, paraffin-embedded tissue blocks of primary or metastatic pancreatic cancer from the pancreas, liver, and lymph nodes were used for immunohistochemical staining. Four-μm-thick tissue sections from the tissue blocks were deparaffinized in xylene and dehydrated using serially dilated ethanol. Endogenous peroxidase was blocked by incubation in 3% H_2O_2 for 10 min; next, heat-induced antigen retrieval was performed. The 10D7G2 monoclonal anti-hENT1 antibody, which is not commercially available[22], and the anti-hENT1 primary antibody (clone SP120, rabbit monoclonal) were used with a BenchMark autostainer (Ventana Medical Systems, Tucson, AZ, USA) according to the manufacturer's protocol. The immunolabeled slides were evaluated by two experienced pathologists blinded to clinical information. Immunohistochemical labeling of the hENT1 protein was semi-quantitatively scored using a previously described histological scoring system that separately considers the size of the stained area and the intensity of the labeling. The intensity was scored as

follows: grade 0, not stained; grade 1, weakly stained; grade 2, moderately stained; grade 3, strongly stained. The labeled area was scored 0 to 4 as follows: 0, no stained area; 1, stained <25%; 2, stained 25%–50%; 3, 51%–75%; 4, >75% of the area stained. The total histological score was calculated by multiplying the area score and the intensity score, producing a range from 0 to 12. The median value of the histological score was 3, which served as the cutoff point for dichotomization. In that way, cases were divided into strong (histological score, >3) and no/weak (histological score, ≤3) hENT1 expression groups. Representative images of strong and no/weak hENT1 expression are depicted in Figure 2.

Comparative analysis

Continuous variables are reported as the mean ± standard deviation or median with min, max values as appropriate and were compared using Student's *t*-test.

Categorical variables were compared using a chi-square test, Fisher's exact test, or

linear-by-linear association test. All tests were two-sided, and a p-value ≤0.05 was considered statistically significant. Univariate and multivariable Cox proportional hazards models were used to identify risk factors for PFS in mPC patients. Variables were excluded through backward selection until only statistically significant variables remained in the final model. Kaplan-Meier survival curves were constructed to estimate the OS and PFS rates. Survival rates were assessed with a log rank test. Statistical analyses were calculated and compared using SPSS 22.0 (IBM Corp., Armonk, NY, USA).

결과 (Results)

Demographics and efficacy

The mean age of the patients was 59.56 years, and 64.1% of them were male. The method of confirmation varied among patients, with 25.5% undergoing excisional biopsy and 74.5% undergoing fine-needle aspiration. In this study, 56.9% of the tissues were obtained from the pancreas, and the remaining 43.1% were collected from other organs, including the liver, small intestine, and lymph nodes. Most patients (98.5%) exhibited an ECOG performance status of 0 or 1. In 37.9% of cases, the primary tumor site included the head of the pancreas. The distribution of metastatic sites varied by patient, with liver metastasis being the most prevalent (64.7%), followed by lymph node metastasis (34.0%), peritoneal metastasis (30.1%), lung metastasis (15.0%), and bone metastasis (3.9%). Multiple metastases were identified in 39.9% of all patients. The median duration of first-line chemotherapy was 5.3 months (range: 0.0 to 22.2 months). Disease progression led to discontinuation of first-line chemotherapy in 70.6%

of the patients. Table 1 shows the baseline characteristics of the patients according to chemotherapy regimen. AG was administered to 78 patients, and 75 patients were treated with FOLFIRINOX. The proportion of males was higher in the FOLFIRINOX group (56.4% vs. 72.0%, *p* value = 0.033). The proportions of lung metastasis (20.5% vs. 9.3%, *p* value = 0.043), distant lymph node metastasis (44.9% vs. 22.7%, *p* value = 0.003), and multiple metastases (52.6% vs. 26.7%, *p* value = 0.001) were higher in the AG group. The FOLFIRINOX group had a higher proportion of patients receiving second-line chemotherapy than the AG group (59.2% vs. 82.7%, *p* value = 0.001), and the type of second-line chemotherapy differed between the two groups. Patients in the AG group were predominantly treated with fluoropyrimidine as a second-line regimen (93.3%), whereas the FOLFIRINOX group was more frequently treated with a gemcitabine-based regimen as second-line chemotherapy (96.8%). The other patient characteristics did not differ between the groups. Table 2 shows the patient characteristics according to hENT1 expression. None of the factors except the site of

metastasis differed between the strong hENT1 group and the no/weak hENT1 group. Liver metastases (76.6% vs. 56.2%, *p* value = 0.007) were more prevalent in patients with strong hENT1 expression, and lung metastases were more common in the no/weak hENT1 group (12.5% vs. 16.9%, *p* value = 0.043). The patient cohort was divided into four distinct groups based on hENT1 expression and first-line chemotherapy regimen. The numbers of patients in the groups were 32 (AG with strong hENT1), 46 (AG with no/weak hENT1), 32 (FOLFIRINOX with strong hENT1), and 43 (FOLFIRINOX with no/weak hENT1). Patients with strong hENT1 expression who were treated with AG were compared with the other three groups (Table 3). The proportion of liver metastasis was higher in the AG with strong hENT1 group than in the AG with no/weak hENT1 expression group (84.4% vs. 45.7%, *p* value = 0.001). No other factors except second-line chemotherapy differed between the AG with strong hENT1 group and the other groups, and the AG with strong hENT1 group had the lowest rate of second-line chemotherapy (54.8%; 62.2% in AG with

no/weak hENT1, *p* value = 0.048; 90.6% in FOLFIRINOX with strong hENT1, *p* value < 0.001; 76.7% in FOLFIRINOX with no/weak hENT1, *p* value < 0.001). The measurable tumor response to first-line chemotherapy is presented in Table 4. The tumor response did not differ significantly between the AG with strong hENT1 group and the other three groups.

Comparative analysis of survival outcomes between patients with strong hENT1 expression treated with AG and other groups.

The median follow up was 11.4 months (range: 0.4 to 43.3 months). The median OS in the AG with strong hENT1 group was 15.4 months (Figure 3). The median OS for the AG with no/weak hENT1 group was 11.1 months, and that for the FOLFIRINOX with strong hENT1 group was 10.4 months. The 1-year OS rate was 63% in the AG with strong hENT1 group, 43% in the AG with no/weak hENT1 group, 38% in the

FOLFIRINOX with strong hENT1 group, and 37% in the FOLFIRINOX with no/weak hENT1 group. The AG with strong hENT1 group demonstrated better median OS and 1-year OS than the other groups, but those differences were not statistically significant (vs. AG with no/weak hENT1 group; p =0.06, vs. FOLFIRINOX with strong hENT1 group; p =0.4). On the other hand, the difference between the AG with strong hENT1 group and FOLFIRINOX with no/weak hENT1 group was statistically significant (15.4 months vs. 10.3 months, p =0.005).

Figure 4 shows the PFS of each group. The AG with strong hENT1 group had longer median PFS than the other groups (7.8 months); however, statistical significance was not observed in comparison with any of the other groups (vs. AG with no/weak hENT1 (6.4 months), p = 0.7; vs. FOLFIRINOX with strong hENT1 (5.7 months), p > 0.999; FOLFIRINOX with no/weak hENT1 (4.9 months), p = 0.1). Figure 5 compares the OS and PFS of patients in the AG with strong hENT1 group with that of patients in the other groups. The AG with strong hENT1 group had better OS and PFS than the

combined patient population of the other three groups. However, significant differences were not observed (OS, p = 0.09; PFS, p = 0.412). Figure 6 shows a Kaplan-Meier curve of survival rate difference based on hENT1 expression among patients who received gemcitabine-based regimens (including AG) as first- or second-line chemotherapy. The median OS and 1-year OS were better in the strong hENT1 group, but the difference was not significant (p = 0.106).

Subgroup analysis of survival outcomes between patients with strong hENT1 expression treated with AG and the other groups.

Given that the patient characteristics varied by group, which could potentially affect the interpretation of hENT1 expression and chemotherapy efficacy, a subgroup analysis was conducted after confirming the risk factors associated with survival

outcomes. In that analysis, the ECOG performance score and liver metastasis were identified as risk factors for progression (Table 5). Identification of risk factors for OS was not possible because all patients in this study had died before the study began. Therefore, the OS subgroup analysis was performed based on liver metastasis and was limited to patients with ECOG 0 or 1 (Figures 7 and 8). The analysis showed that the AG with strong hENT1 group had a statistically better OS than the AG with no/weak hENT1 group (15.7 months vs. 10.8 months, $p = 0.023$). The median PFS was also better in the AG with strong hENT1 group, but the difference was not significant (7.4 months vs. 5.5 months, $p = 0.081$). The AG with strong hENT1 group also had statistically better OS than the FOLFIRINOX group (15.7 months vs. 9.3 months, $p = 0.040$). However, PFS did not differ significantly between those groups (7.4 months vs. 4.7 months, $p = 0.514$). The AG with no/weak hENT1 group and FOLFIRINOX group did not differ significantly in OS or PFS (10.8 months vs. 9.3 months, $p = 0.797$; 5.5 months vs. 4.7 months, $p = 0.569$, respectively). On the other hand, in a subgroup

analysis of patients with an ECOG of 0 or 1 and no liver metastasis, the AG with strong hENT1 and AG with no/weak hENT1 groups did not differ significantly in OS (13.0 months vs. 11.9 months, $p = 0.563$) or PFS (9.3 months vs. 8.8 months, $p = 0.582$). Furthermore, the AG with strong hENT1 group and the FOLFIRINOX group did not differ significantly in OS (13.0 months vs. 11.7 months, $p = 0.897$) or PFS (9.3 months vs. 6.1 months, $p = 0.381$).

고찰 (Discussion)

In this study, the metastatic site distribution among patients with mPC varied based on the expression level of hENT1. Specifically, patients with strong hENT1 expression had a higher incidence of liver metastases, whereas those with no/weak hENT1 expression were more likely to develop lung metastases. mPC frequently involves the liver as the primary site of metastasis, followed by the peritoneum, lung, and lymph nodes in that order[23]. However, little research has investigated whether hENT1 expression affects the pattern of metastasis in this disease. A study that evaluated recurrence patterns based on hENT1 expression after pancreatectomy did not reveal any significant differences between patients with strong hENT1 expression and those with no/weak hENT1 expression[24]. However, that study sample was limited to patients treated with surgical intervention, and the sample size was relatively small, which might have affected the statistical power of the analysis. Despite extensive research efforts, the underlying mechanisms of liver metastasis in pancreatic cancer

remain poorly understood. Although Wang, Z. et al. reported genetic differences between liver and lung metastases in colorectal cancer[25], research investigating similar differences in pancreatic cancer remains scant. Recently, a report indicated that activation of NOTCH3 by the transcription factor GATA2 can promote liver metastasis in pancreatic cancer[26]. However, the relationship between hENT1 expression and liver metastasis in pancreatic cancer remains unexplored. Therefore, additional studies are needed to elucidate the relationship between gene expression patterns and metastasis in pancreatic cancer. Understanding the molecular mechanisms involved in pancreatic cancer metastasis, including the potential role of hENT1 expression, could have important clinical implications for patient treatment.

The findings of this study indicate that mPC patients who have strong hENT1 expression and are treated with the AG regimen have better survival times than patients with no/weak hENT1 expression who receive the AG regimen or the FOLFIRINOX regimen under certain conditions. The median OS was better in the AG with strong

hENT1 group than the FOLFIRINPOX with no/weak hENT1 group. Among mPC patients of ECOG 0 or 1 with liver metastasis, the median OS of the AG with strong hENT1 group was better than that of the AG with no/weak hENT1 group and both FOLFIRINOX groups. Previous studies have reported findings similar to those reported here. Higher expression levels of hENT1 were previously associated with a higher response to gemcitabine in pancreatic cancer[16]. Perera, S. et al. reported that advanced pancreatic cancer patients with high hENT1 treated with AG had better median OS (10.6 months) than those with low hENT1 and treated with AG (6.7 months)[20]. Likewise, in the ESPAC-3 trial, the median OS for patients in the high hENT1 expression group who were treated with gemcitabine was 26.2 months, whereas it was 17.1 months in the low hENT1 expression group[27]. Yang, L. et al. reported that AG and FOLFIRINOX showed comparable efficacy outcomes in patients with mPC[28]. A randomized phase II study of modified FOLFIRINOX versus AG reported that AG had better response rate and CA19-9 level, milder gastrointestinal

toxicity, and higher efficacy in terms of 1-year survival[29]. Several past publications and the results of this study indicate that the AG regimen can be considered the first-line treatment for patients with mPC. Furthermore, it can be prioritized over other chemotherapy in mPC patients whose hENT1 expression is strong.

It is important to acknowledge that the interpretation of the results from this study might have limitations. Previous studies have raised concerns about the efficacy of the SP120 anti-hENT1 monoclonal antibody. In the AIO-PK0104 phase III trial, Ormanns, S. et al. reported finding no evidence to support the use of hENT1 as a predictive biomarker for gemcitabine efficacy[30]. In the CONKO-001 trial, hENT1 expression, analyzed using the SP120 antibody, was not predictive of outcomes in patients with pancreatic cancer who were treated with adjuvant gemcitabine[31]. Svrcek, M. et al. reported that concordance between the murine anti-hENT1 antibody (10d7G2), which is not commercially available, and SP120 was found in only 50% of cases[22]. On the other hand, several studies have reported that the SP120 antibody does have clinical

utility as a biomarker for predicting hENT1 expression. In a study comparing the value of SP120 and 10DPG72 for predicting gemcitabine sensitivity in 227 pancreatic cancer patients treated with gemcitabine, both antibodies were useful[32]. Okamura, Y. et al. reported that the response to adjuvant gemcitabine was a significant predictor of patients with low hENT1 expression, as found using either 10D7G2 or SP120[33]. When evaluating hENT1 expression using SP120 in pancreatic cancer patients treated with gemcitabine who participated in the RTOG-904 phase III trial, Poplin, E. et al. reported that the high hENT1 group had a better survival rate than the other groups[34]. Consequently, additional antibody development is needed to assess hENT1 expression, and ongoing validation of the anti-hENT1 monoclonal antibodies presently used in this capacity is essential.

The inclusion of not only the primary site, but also metastatic sites for the tissue biopsy analysis in this study suggests the need for careful consideration in interpreting the findings. Numerous studies have reported that metastatic lesions exhibit genetic

features distinct from those of the primary tumor site. Niedergethmann et al. identified 25 genes significantly upregulated and 181 genes significantly downregulated when comparing liver metastases with a primary pancreatic cancer[35] in a mouse model. Hata, F. et al. found a difference in the parental cell line expression pattern in liver and peritoneal metastases of pancreatic cancer[36]. However, a previous report comparable to this study evaluated the mRNA expression levels of hENT1 in pancreatic cancer patients, most of whom (86.4%) had mPC[20]. Tissue samples in that study were primarily collected from metastatic lesions in the liver, and it reported a significant association between elevated hENT1 expression level and high sensitivity to AG therapy in mPC, consistent with the results reported here. Furthermore, Raffenne et al. reported that the assessment of hENT1 expression at the metastatic site and the primary tumor had a concordance rate of 83%[37]. In our study, the distribution of tissue collection sites did not differ by subgroup. These results lend support to the validity of the current research findings.

The differences in the proportion and regimen of patients who received second-line chemotherapy in the subgroup analysis must be considered when interpreting these results. Numerous studies have reported a statistically significant difference in OS rates between patients who received secondary chemotherapy and those who received conservative treatment following first-line chemotherapy. A meta-analysis reports more frequent recommendation of secondary chemotherapy than of best supportive care after failure of primary chemotherapy in gastric cancer patients[38]. A randomized clinical trial showed that oxaliplatin, folinic acid, and 5-FU significantly prolonged survival times compared with supportive care alone after failure of first-line chemotherapy with gemcitabine[39]. The administration of a gemcitabine-based regimen as second-line chemotherapy in patients who received first-line FOLFIRINOX might have introduced confounding variables into the results of this study. However, the patients who received gemcitabine-based second-line chemotherapy after FOLFIRINOX typically received either gemcitabine monotherapy

or a combination of gemcitabine and erlotinib because AG therapy is not approved for use as second-line chemotherapy by the Korean national health insurance[11]. Furthermore, although lack of secondary chemotherapy was most frequent among the group of patients with strong hENT1 expression who received AG, our results suggest that AG might be more effective and lead to improved survival rates in patients with strong hENT1 expression.

In this study, the prognostic factors were liver metastasis and ECOG score. In the article that served as the basis for this study, a multivariate analysis identified CA19-9 level and liver metastasis as prognostic factors[11]. Zhang, L. et al. reported that mPC patients with liver metastases tended to have a worse prognosis than those with lung metastases[40]. To evaluate the efficacy of AG based on hENT1 expression in mPC patients, it is necessary to conduct a randomized controlled trial with a large sample or to perform subgroup analyses based on different prognostic factors. Such an analysis would help to determine whether AG is effective in patients with strong

hENT1 expression while taking into account other factors that might affect patient prognosis. Therefore, we conducted a subgroup analysis of only patients with liver metastasis and ECOG 0 or 1. The results revealed that patients with strong hENT1 expression who received AG therapy had better OS than the other patient groups. That finding provides a rationale for considering AG over FOLFIRINOX in patients with strong hENT1 expression. Moreover, these results suggest the need for a randomized clinical trial to compare AG and FOLFIRINOX as first-line chemotherapy regimens in patients with strong hENT1 expression who have advanced pancreatic cancer or mPC. Similarly, randomized clinical trials are needed to determine the optimal neoadjuvant chemotherapy approach for patients with strong hENT1 expression who are being considered for surgery.

Our study is limited by its retrospective and non-randomized nature, which increases the likelihood of selection bias and confounding variables that could affect the results. Also, in our subgroup analysis, the number of patients in each group was too small to

achieve statistical significance. The use of SP120 as the anti-hENT1 monoclonal antibody is another limitation of this paper as previously mentioned. Careful interpretation of the results is needed because the advantages of the AG with strong hENT1 group over the other groups were primarily observed in OS, rather than PFS. But although the difference was not statistically significant, the AG with strong hENT1 group demonstrated a better median PFS than the other patient groups, and clear superiority in OS was observed. Therefore, our findings suggest a certain level of validity of the assertion that AG has a more favorable effect in the strong hENT1 group. Nonetheless, further research and larger-scale clinical trials are needed to confirm these results.

Despite the limitations, this study is noteworthy for including a large sample of patients with mPC and for being one of the few studies to compare the efficacy of AG and FOLFIRINOX, particularly based on hENT1 expression. These findings are significant because they can serve as a basis for selecting the appropriate

chemotherapy regimen for patients with pancreatic cancer. These study results provide evidence to suggest that AG therapy could be considered for patients with high hENT1 expression, not only those with mPC, but also in the context of adjuvant chemotherapy following complete resection and neoadjuvant chemotherapy regimens for borderline resectable and locally advanced pancreatic cancer. Subgroup analysis based on prognostic factors is a meaningful approach because it considers the specific characteristics of mPC. Furthermore, this study is the first to demonstrate that AG might be more effective than FOLFIRINOX in the specific patient subgroup with strong hENT1 expression.

결론 (Conclusion)

AG is effective in improving the survival times of mPC patients with strong hENT1 expression. Specifically, mPC patients with strong hENT1 expression, ECOG 0 or 1, and liver metastasis who were treated with AG had longer OS than patients with no/weak hENT1 expression who received AG and patients treated with FOLFIRINOX, regardless of hENT1 expression.

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영문요약

Introduction

The standard first-line chemotherapy regimens for advanced pancreatic cancer are nab-paclitaxel and gemcitabine (AG) and 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). However, inadequate research has compared the effectiveness of these two regimens in the context of heightened expression of hENT1, a transporter that facilitates the uptake of gemcitabine. Thus, the objective of this study was to retrospectively evaluate the efficacy of AG and FOLFIRINOX in patients with metastatic pancreatic cancer (mPC) based on hENT1 expression.

Methods

From 2013 to 2016, 153 mPC patients treated with AG or FOLFIRINOX in a large-volume single institution were retrospectively analyzed. The patients were classified into groups based on hENT1 expression and first-line chemotherapy regimen. The

overall survival (OS) and progression-free survival (PFS) of each group were compared. After identifying the prognostic risk factors, a secondary subgroup comparison was performed by adjusting for those factors in each group.

Results

Demographically, the strong hENT1 group exhibited a higher percentage of liver metastasis than the no/weak hENT1 group (76.6% vs. 56.2%, p =0.007) and a lower percentage of lung metastasis (12.5% vs. 16.9%, p =0.043). The median OS was better in the AG with strong hENT1 group than in the FOLFIRINOX with no/weak hENT1 group (15.4 months vs. 10.3 months, p =0.005). ECOG 2 and liver metastasis were identified as risk factors for prognosis, and the subgroup analysis of patients with ECOG 0 or 1 and liver metastasis who received AG revealed that the group with strong hENT1 expression had a longer OS than the group with no/weak hENT1 expression (15.7 months vs. 10.8 months, p = 0.021) and the FOLFIRINOX group (15.7 months vs. 9.3 months, p = 0.040).

Conclusion

AG is effective chemotherapy in mPC patients with strong hENT1 expression. AG should especially be considered as a first-line regimen in mPC patients with strong hENT1 expression and ECOG 0/1 and liver metastasis.