Analysis of Clinical Predictive Factors Affecting the Outcome of 2nd Line Chemotherapy for the Patient of Advanced Pancreatic Cancer

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Directed by Professor Seungmin Bang

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Analysis of Clinical Predictive Factors Affecting the Outcome of 2nd Line Chemotherapy for the Patient of Advanced Pancreatic Cancer.

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Objective: Benefit of second line chemotherapy (SL) after failed first-line chemotherapy (FL) in advanced pancreatic cancer has not yet been established. We intend to identify prognostic factors and ultimately devise a model of clinical parameters for decision of SL versus basic supportive care (BSC) after failure of FL.

Methods: Patients who received gemcitabine based FL for advanced pancreatic cancer at Yonsei University Hospital between January 2010 and December 2015 were retrospectively reviewed. Significant clinical parameters regarding SL related survival were reviewed for analyzing predictive factors.

Results: Prognostic factors significant to OS2 were metastasis at peritoneum ($p<0.001$), number of metastasis ($p<0.001$), thrombosis event ($p=0.003$) and level of CA19-9 ($p=0.011$). Harrall's C-index of the final prognosis prediction model was 0.62. We made an attempt to devise a prognostic nomogram to predict the benefit of SL.

Conclusion: SL may be beneficial for patients without peritoneum metastasis and thrombotic event during FL, single lesion of metastasis and level of CA19-9 under 90U/mL. This prognostic nomogram can be used to predict OS2 before administration of SL and may help clinicians with therapeutic decisions.

Key words : Pancreatic cancer, Second line chemotherapy, Prognostic model

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I. INTRODUCTION

Pancreatic cancer is a leading cause of cancer death worldwide with an estimated 5 year survival rate of 5-6%.[1,2] For the past decade, gemcitabine has been considered as the standard first line chemotherapy(FL) in locally advanced and metastatic pancreatic cancer, demonstrating the improvement of overall survival.[3] Despite the substantial development in palliative chemotherapies, the median overall survival is still less than 8 months with frequent resistance in first line chemotherapy.[4,5] Various second line chemotherapies (SL) have been associated with improved overall survivals in patients who have experienced progression while receiving gemcitabine.[6] Currently, the CONKO-003 study presented the OFF regimen including oxaliplatin, folinic acid and 5-FU, as an effective SL therapy after gemcitabine treatment failure, proving significant improvement in overall survival.[7] However, there are no other large randomized studies available to establish the consensus of SL chemotherapy after disease progression of FL treatment. Furthermore, there is no evidence proving the superiority of second line treatment with basic supportive care after failure of first line treatment failure.[8,9] Our study was to analyze the clinical characteristics of patients who have received SL therapy or discontinued salvage chemotherapy and went on with

best supportive care (BSC) after FL treatment. The primary endpoint was to evaluate clinical characteristics affecting the benefits from receiving SL therapy comparing to BSC. The second endpoint of our study was to establish a prognostic scoring system for an optimal decision of proceeding SL after the failure of gemcitabine based FL.

II. MATERIALS AND METHODS

1. Patients

All patients with histologically proven pancreatic adenocarcinoma (metastatic and recurrent after surgery) treated at Gastroenterology Unit of Yonsei University Hospital, Seoul, South Korea, between January 2010 and December 2015 were involved in the development cohort. Patients were considered eligible for medical evaluation of SL indication if they had received one previous line of gemcitabine based FL, including gemcitabine based adjuvant chemotherapy in the case of operation received patients. The external validation cohort included patients with pancreatic adenocarcinoma who received gemcitabine based FL in the same institution as development cohort between January 2016 and December 2016.

2. Methods

Clinical, biological, and radiological parameters of the data were measured at the beginning of second line chemotherapy or at the end of first line chemotherapy for patients who proceeded with best supportive care. Treatment outcomes were retrospectively collected from medical records.

Overall survival (OS) was calculated from the date of initiation of FL to the date of death from any cause. Overall survival 2 (OS2) was calculated from the date of first administration of SL to the date of death from any cause. For Patients who only received FL and went on with BSC after progression, OS2 was measured from the end of FL to death of any cause. For patients with history of curative operation, OS2 was measured from the date of first line palliative chemotherapy to the date of death from any cause.

3. Statistical analysis

Median value (interquartile range) and frequency (percentage) were provided for the description of continuous and categorical variables, respectively. Medians and proportions were compared using Student's t test and chi-square test (or Fisher's exact test, if appropriate), respectively. Cox proportional hazard models were performed to estimate hazard ratio (HR) and 95% confidence interval for prognostic factors associated with OS2. The association of baseline parameters of OS2 was first assessed by dividing the patient in two groups by OS2; 6 months below and 6 months above. Additionally, baseline parameters of OS2 was assessed by univariate Cox analyses, and then parameters with P values of less than 0.05 were entered into the final multivariable Cox regression model, after considering collinearity among variables with a correlation matrix.

Sensitivity analysis to explore the reliability of the final prognosis predictive model was performed with a stratified and a frailty approach by using a random component for the hazard function based on the regimen, and with a full-model and forward procedure. Accuracy of the final model was verified regarding the discrimination parameter. The predictive value and the discrimination ability of the final model were assessed with the Harrell's concordance index (C-index). Random samples of the cohort were used to derive 95% confidence interval bootstrap percentile for the C-statistics. Internal validation of the final model was performed with a bootstrap sample procedure.

The prognostic score was constructed with nomogram total points. The prognostic score discrimination ability was confirmed in internal and external validation cohort and evaluated with the C-index. To identify risk groups and determine their survival benefit with SL, the same development cohort derived risk predictive algorithm was applied. A clinical benefit centered accuracy of the final model was evaluated by a decision curve analysis for both cohorts.

All analyses were performed using SPSS version 23.0 and R software version 2.15.2 (R Development Core Team, Vienna, Austria; http://www.r-project. org).

P values were calculated 2-sided and less than 0.05 were considered statistically significant.

III. RESULTS

1. Characteristics of SL Group Compared to BSC Group after FL Failure

The median overall survival of SL patients versus BSC patients was 40weeks (range, 28.0-56.0) versus 16.0weeks (range, 12.0-32.0). The median overall survival after the progression of first line chemotherapy of SL group (OS2) was 20.0weeks (range, 12.0-32.0). The median duration of basic supportive care of FL only group after progression of first line chemotherapy (OS2) was 8.0weeks (range, 4.0-16.0).

There was significant difference in gender between two groups (evaluable in 501 patients; Male SL 47.3% versus BSC 62.9%; P = 0.001). The ECOG PS (ECOG PS: Eastern Cooperative Oncology Group Performance Status) was significantly higher in SL patients at the initiation of palliative SL chemotherapy (evaluable in 501 patients; ECOG 0: SL 83.7% versus BSC 61.7%; P < 0.001). There was a significant difference in primary tumor localization between two groups (evaluable in 501 patients; localization at head: SL 52.2% versus BSC 38.3%; P =0.002)

Significantly higher number of SL patients received longer duration of FL treatment (evaluable in 501 patients; SL group median 16.0weeks (range 8.0-26.0) versus BSC median 8.0weeks (range 4.0-16.0); P < 0.001). Significantly more patients in the SL group was diagnosed with metastasis at lung (SL 20.4% versus BSC 10.5%; P = 0.003) and peritoneum (SL 32.7% versus BSC 40.8%; P = 0.001).

No significant differences were detected between SL group and BSC group regarding age, metastatic lesion (liver, bone, distant lymph node and other sites including adrenal gland at spleen), number of metastasis after FL progression,

preexisting diabetes, thrombosis event during FL therapy and BMI. Moreover, there was no significant difference in tumor markers CA 19-9. (Table 1.)

Table1. Baseline Characteristics of BSC Patients (n=256) and SL Patients (n=245) after FL Progression

Characteristics	Best Supportive Care (n=256) Median, N(%)	Second Line chemotherapy (n=245) Median, N(%)	P value
Gender (Male)	161(62.9%)	116(47.3%)	0.001
Age	64.0(55.0-71.0)	62.0(55.5-69.0)	0.151
ECOG PS 0	158(61.7%)	205(83.7%)	<0.001
Tumor localization			0.002
Head	98(38.3%)	128(52.2%)	
Body and tail	142(55.5%)	98(40.0%)	
Overlapping	16(6.3%)	19(7.8%)	
Metastatic lesion			
Liver	174(68.0%)	168(68.6%)	0.924
Lung	27(10.5%)	50(20.4%)	0.003
Bone	21(8.2%)	11(4.5%)	0.102
Other	24(9.4%)	18(7.3%)	0.426
Distant lymph node	35(13.7%)	50(20.4%)	0.056
Peritoneum	123(40.8%)	80(32.7%)	0.001
Number of Metastasis			0.929
Single	138(53.9%)	131(53.5%)	
Multiple	118(46.1%)	114(46.5%)	
FL duration (week)	8.0(4.0-16.0)	16.0(8.0-26.0)	<0.001
OS (week)	16.0(12.0-32.0)	40.0(28.0-56.0)	<0.001
OS2 (week)	8.0(4.0-16.0)	20.0(12.0-32.0)	<0.001
Diabetes mellitus	81(31.6%)	95(38.8%)	0.111
Thrombosis	30(11.7%)	31(12.7%)	0.786
CA 19-9 > 90.0U/mL	193(75.4%)	157 (64.1%)	0.006
BMI	22.2(20.32-23.60)	22.7(21.95-23.82)	0.335
SL Type			
FOLFIRINOX		90 (36.7%)	
FOLFOX		29 (11.8%)	
XELODA+XELOX		98 (40.0%)	
FEP		28 (11.4%)	

ECOG: Eastern Cooperative Oncology Group; FL: First Line Chemotherapy; OS: Overall survival ; OS2: Overall survival 2; CA 19-9: Carbohydrate Antigen 19-9; BMI: Body Mass Index; SL: Second Line Chemotherapy

2. Characteristics of SL Group with or without History of Curative Operation

The median OS of SL patients with operation versus SL patients without operation was 44.0weeks (range, 24.5-67.0) versus 36.0weeks (range, 28.0-56.0). The median OS2 of SL group with operation versus SL patients without operation was 20.0weeks (range, 8.0-47.0) versus 20.0weeks (range, 12.0-32.0). The ECOG PS at the start of palliative SL was significantly higher in SL patients with operation (evaluable in 245 patients; ECOG 0: SL with operation 100.0% versus SL without operation 77.9%; $P < 0.001$). There was a significant difference in primary tumor localization between two groups (evaluable in 245 patients; localization at head: with operation 82.8% versus without operation 41.4%; $P < 0.001$). There was a significant difference in median FL duration in two groups (evaluable in 245 patients; SL with operation 20.0 weeks (range, 13.0-28.0). versus SL without operation 14.0 (range; 6.0-28.0); $P = 0.002$).

No significant differences were detected between two groups regarding gender, age, metastatic lesion including peritoneum, number of metastasis after FL progression, preexisting diabetes, thrombosis event during FL therapy and BMI. Moreover, there was no significant difference in tumor markers CA 19-9.

Table2. Baseline Characteristics of Curative Operation Received Patients (n=64) in SL Patients (n=245)

Characteristics	Without Operation (n=181) Median, N(%)	With Operation (n=64) Median, N(%)	P value
Gender (Male)	83(44.4%)	37(57.8%)	0.111
Age	62.0(55.0-69.0)	63.0(56.0-70.0)	0.070
ECOG PS 0	141(77.9%)	64(100%)	<0.001
Tumor localization			<0.001
Head	75(41.4%)	53(82.8%)	
Body and tail	88(48.6%)	10(5.61%)	

Overlapping	18(9.9%)	1(1.6%)	
Metastatic lesion			
Liver	126(69.6%)	42(65.6%)	0.639
Lung	41(22.7%)	9(14.1%)	0.154
Bone	11(6.1%)	0(0.0%)	0.071
Other	12(6.6%)	6(9.4%)	0.577
Distant lymph node	29(16.0%)	21(32.8%)	0.006
Peritoneum	59(32.6%)	21(32.8%)	1.000
Number of Metastasis			0.561
Single	99(54.7%)	32(50.0%)	
Multiple	82(45.3%)	32(50.0%)	
FL duration (week)	14.0(6.0-28.0)	20.0(13.0-28.0)	0.002
OS (week)	36.0(28.0-56.0)	44.0(24.5-67.0)	0.117
OS2 (week)	20.0(12.0-32.0)	20.0(8.0-47.0)	0.020
Diabetes mellitus	68(36.4%)	45(42.5%)	0.304
Thrombosis	24(12.8%)	15(14.2%)	0.750
CA 19-9 >90.0U/mL	127(70.2%)	30(46.9%)	0.001
BMI	23.3(22.10-24.10)	22.5(21.12-23.37)	0.065
Stage before operation			
IB		1 (1.6%)	
IIA		23 (35.9%)	
IIB		38 (59.4%)	
III		2 (3.1%)	
Operation type			
Total Pancreatectomy		1(1.6%)	
PPPD		51(79.7%)	
Distal Pancreatectomy		12(18.8%)	

ECOG: Eastern Cooperative Oncology Group; FL: First Line Chemotherapy; OS: Overall survival ; OS2: Overall survival 2; CA 19-9: Carbohydrate Antigen 19-9; BMI: Body Mass Index; SL: Second Line Chemotherapy

3. Characteristics of 6months below OS2 SL Group Compared to 6 months above OS2 SL Patients: Determinants of OS2 in SL group

SL patient was divided into two groups depending on the OS2 duration: OS2 below 6 months and above 6months. The median OS2 of 6months below group was 12.0weeks (range, 8.0-24.0). The median OS2 of 6months above group was 36.0weeks (range, 28.0-52.0).

Number of metastasis was a significant parameter between two groups (evaluable in 245 patients; single metastasis; OS2 below 6months; 42.0% versus OS2 above 6 months; 68.2%; multiple metastasis; OS2 below 6months; 58.0% versus OS2 above 6 months; 31.8%; P <0.001).

Metastasis at peritoneum was significantly higher in OS2 6 months below group (evaluable in 245 patients; carcinomatosis; OS2 below 6months; 43.5% versus OS2 above 6 months; 18.7%; P <0.001).

Thrombotic event was significantly higher in OS2 6 months below group (evaluable in 245 patients; thrombus event; OS2 below 6months; 18.1% versus OS2 above 6 months; 5.6%; P =0.003).

CA 19-9 measured after FL progression was significantly higher in OS2 6 months below group (evaluable in 245 patients; CA 19-9>90U/mL; OS2 below 6months; 71.0% versus OS2 above 6 months; 55.1%; P =0.011).

No significant differences were detected between two groups regarding gender, age, ECOG PS, primary tumor localization, metastatic lesion besides peritoneum, FL duration, preexisting diabetes, BMI, curative operation and regimen type of SL. (Table 3.)

Table3. Baseline Characteristics of OS2 below 6 months (n=138) and above 6 months (n=107) with SL Group

Characteristics	OS2 6 months below (n=138) Median, N(%)	OS2 6 months above (n=107) Median, N(%)	P value
Gender (Male)	65(47.1%)	55(51.4%)	0.522
Age	64.0(56.0-69.0)	61.0(55.0-68.0)	0.076
ECOG PS 0	110(79.7%)	95(88.8%)	0.145
Tumor localization			0.451
Head	68(49.3%)	60(56.1%)	
Body and tail	60(43.5%)	38(35.5%)	
Overlapping	10(7.2%)	9(8.4%)	
Metastatic lesion			
Liver	101(73.2%)	67(62.6%)	0.096
Lung	26(18.8%)	24(22.4%)	0.525
Bone	4(2.9%)	7(6.5%)	0.218

Other	10(7.2%)	8(7.5%)	1.000
Distant lymph node	29(21.0%)	21(19.6%)	0.873
Peritoneum	60(43.5%)	20(18.7%)	<0.001
Number of Metastasis			<0.001
Single	58(42.0%)	73(68.2%)	
Multiple	80(58.0%)	34(31.8%)	
FL duration (week)	16.0(8.0-24.0)	20.0(12.0-32.0)	0.108
OS (week)			
OS2 (week)	12.0(8.0-24.0)	36.0(28.0-52.0)	<0.001
Diabetes mellitus	52(37.7%)	43(40.2%)	0.694
Thrombosis	25(18.1%)	6(5.6%)	0.003
CA 19-9 > 90.0U/mL	98(71.0%)	59 (55.1%)	0.011
BMI	22.5(20.90-23.67)	23.4(22.20-24.30)	0.187
Curative Operation	36 (26.1%)	28(26.2%)	0.989
Second Line Type			0.217
FOLFIRINOX	45(32.6%)	46 (43.0%)	
FOLFOX	15(10.9%)	13 (12.1%)	
XELODA+XELOX	63(45.7%)	35 (32.7%)	
FEP	15(10.9%)	13 (12.1%)	

ECOG: Eastern Cooperative Oncology Group; FL: First Line Chemotherapy; OS: Overall survival ; OS2: Overall survival 2; CA 19-9: Carbohydrate Antigen 19-9; BMI: Body Mass Index; SL: Second Line Chemotherapy

4. Univariate and Multivariate Analysis for OS2

Univariate analysis revealed ECOG performance status, metastasis in peritoneum, number of metastasis, FL duration, thrombosis event, CA 19-9 level above 90U/mL and BMI were significant independent prognostic factors for OS2 ($P< 0.05$). Therefore, the factors were included in the multivariate analysis.

In the multivariate analysis, more than one site of metastasis lesion, thrombosis event during FL and CA 19-9 level above 90U/mL were significantly independent prognostic factors for OS2 for all 245 patients ($P< 0.05$). (Table 4.)

Table 4. Univariate and Multivariate Analysis for OS2 in SL Group (n=245)

	Univariate OS Hazard ratio (95%confidence interval)	Univariate OS P value	Multivariate OS Hazard ratio (95%confidence interval)	Multivariate OS P value
Gender	1.059(0.822-1.363)	0.659		
Age	1.011(0.997-1.026)	0.121		
ECOG PS				
0	ref	ref	ref	ref
>1	0.400(0.164-0.978)	0.044	1.364(0.933-1.992)	0.109
Tumor localization				
Head	ref	0.057		
Body and tail	0.812(0.499-1.322)	0.403		
Overlapping	1.128(0.690-1.845)	0.631		
Metastatic lesion				
Liver	1.232(0.96201.57)	0.099		
Lung	1.024(0.764-1.372)	0.876		
Bone	0.978(0.548-1.747)	0.941		
Other	0.830(0.536-1.285)	0.404		
Distant lymph node	0.994(0.744-1.328)	0.967		
Peritoneum	1.622(1.236-2.127)	<0.001	1.253(0.924-1.698)	0.147
Metastasis Number				
Single	0.621(0.481-0.802)	<0.001	0.694(0.520-0.926)	0.013
Multiple	ref	ref	ref	ref
SL type				
FOLFIRINOX	ref	ref	ref	ref
FOLFOX	0.776(0.506-1.190)	0.245	1.605(1.023-2.518)	0.040
XELODA+XELOX	1.151(0.680-1.949)	0.601	1.710(1.233-2.372)	0.001
FEP	1.381(0.904-2.110)	0.135	1.500(0.955-2.355)	0.078
FL duration (week)	0.988(0.979-0.997)	0.012	0.991(0.982-1.001)	0.074
Diabetes mellitus	0.830(0.655-1.051)	0.123		
Thrombosis	1.789(1.219-2.626)	0.003	1.391(0.929-2.082)	0.035
CA 19-9	0.662(0.504-0.868)	0.003	1.184(0.881-1.591)	0.025
<90.0U/mL	ref	ref	ref	ref
CA19-9 >90.0U/mL				
BMI	0.926(0.861-0.995)	0.037	0.940(0.875-1.010)	0.090
Curative Operation	0.766(0.568-1.033)	0.081		

ECOG: Eastern Cooperative Oncology Group; FL: First Line Chemotherapy; OS: Overall survival ; OS2: Overall survival 2; CA 19-9: Carbohydrate Antigen 19-9; BMI: Body Mass Index; SL: Second Line Chemotherapy

5. Prognostic Nomogram and Prediction of the Survival Benefit of SL

The prognostic nomogram was devised with all statistically significant independent factors from the analysis of OS2 groups divided by duration of 6 months (Figure 1). Number of metastasis lesion, thrombosis event during FL and CA 19-9 were the final determinants integrated to the nomogram. The prognostic score was based on the total number of points obtained from the nomogram. (Figure 1.)

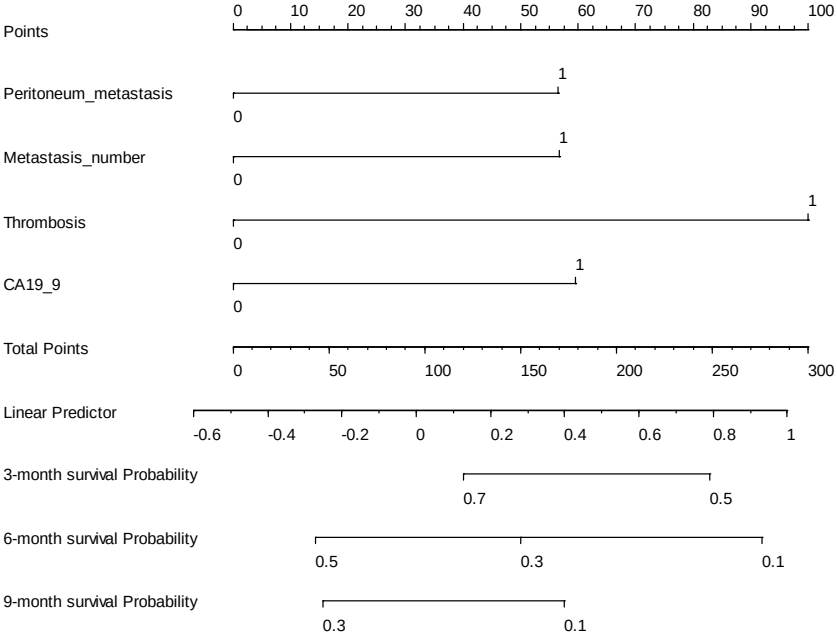

Figure 1. Prognostic Nomogram to Predict Individual OS2 probability

No Peritoneum metastasis : 0 Peritoneum metastasis :1 ; Single metastatic lesion :0 Multiple metastatic lesion :1; No thrombosis event :0 Thrombosis event :1 ; CA19-9 <90U/mL :0 CA19-9>90U/mL:1

Prognostic nomogram to predict individual OS2 probability at the beginning of second-line chemotherapy in patients with advanced pancreatic cancer. First, the points associated with each of the four prognostic factors are obtained via upward vertical translation of the patient's variable

value to the line labeled “Points.” Next, the points are summed and the corresponding total number is reported as a dot on the line labeled “Total points.” A vertical line is then drawn downward from the total point dot to obtain the OS2 prediction at the intersection with the “3-,” “6-,”and “9-month survival probability” lines.

6. Confirmation of the Prediction Model with Prognostic Subgroups

We identified three prognostic subgroups with the nomogram scoring: “good” prognosis (score 0-60). “intermediate” prognosis (score 116-160), and “poor” prognosis (score 176-276). Good prognosis group included: none of the four determinants (score 0), only peritoneum metastasis (score 58), only single metastasis (score 58), only CA19-9 above 90U/mL (score 60). Poor prognosis group included three out of four determinants (score 176, 218) and all four determinant (maximum score 276). This deverlopment cohort confirmed that the predefined prognostic subgroups “good,” “intermediate,” and “poor” reflected the expected survival after the FL failure with a median OS2 of 28.0weeks (95%CI, 25.2—30.8), 18.0weeks (95% CI, 15.8–210.2), and 12.0weeks (95% CI, 10.7-13.3), respectively ($P < 0.001$). Such grouping achieved a clear separation of the Kaplan–Meier curves (Figure 2).

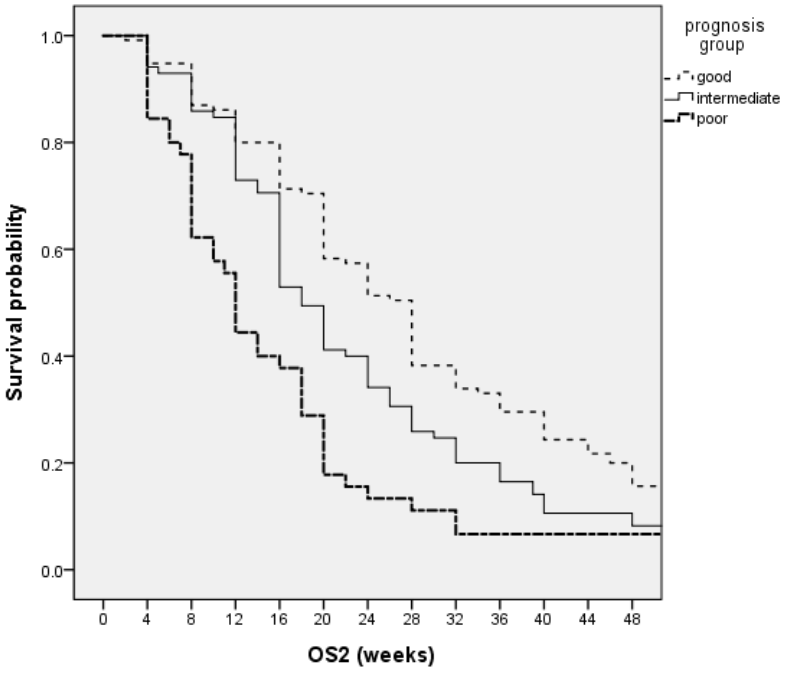

Figure2. Kaplan-Meier curves of OS2 for the prognostic subgroups "poor-intermediate-good" in the development cohort

7. Internal Validation and External Validation of the Final Nomogram

In the internal validation, uncertainties around hazard ratio measured with a bootstrapping procedure reflected the robustness of the final model. The input of three parameters identified in the final model; number of metastasis lesion, thrombosis event during FL and CA 19-9 level. The discrimination ability of the final model developed in the main analysis was internally confirmed (C-index= 0.62, 95% CI = 0.58 to 0.69). The iAUC curve of the development cohort was 0.619. (Figure 2). Data of the three baseline parameters that were required for the nomogram calculation was available for 123 patients from the external validation cohort (C-index= 0.56, 95% CI = 0.54 to 0.60). The iAUC curve of

the external validation cohort was 0.561 (Figure 3.) As expected, the external validation cohort differed from the development cohort.

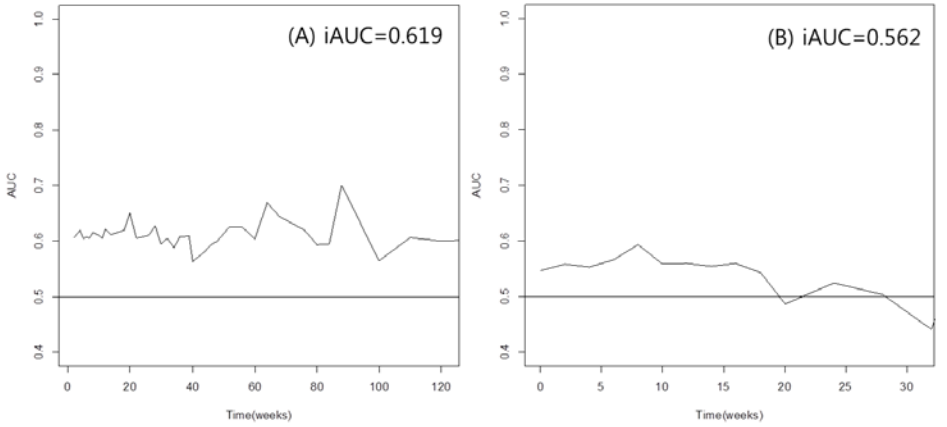

Figure3. Internal Validation iAUC (A) and External Validation iAUC (B) of the Prognostic Nomogram

IV. DISCUSSION

Generally, pancreatic cancer progresses rapidly and patient's performance status often deteriorates too rapidly to perform any additional salvage chemotherapy after the failure of first line chemotherapy.[10,11] Furthermore, second line chemotherapy should be started with more caution than first line therapy, since patients may suffer from fatal adverse effects.[12]

Current guideline for advanced pancreatic cancer recommends second line chemotherapy after disease progression under first line chemotherapy. Still, the benefit of second line chemotherapy remains a controversial issue.[13] CONKO-003 study, an open randomized phase 3 study, proved that the combination of oxaliplatin, 5-FU, and folinic acid (OFF regimen) after previous gemcitabine based chemotherapy resulted a significant extension of progression free survival(PFS) and overall survival in comparison to best supportive care after the progression under first line chemotherapy. In this phase III trial (CONKO-

003) including 160 gemcitabine pre-treated patients with advanced pancreatic cancer, patients receiving OFF regimen achieved a median PFS of 13 weeks (P= 0.012) and a median overall survival of 26 weeks (P= 0.014), compared with 9 and 13 weeks.[7] However, there is no other greater evidence to support the efficacy of optimal second line chemotherapy for gemcitabine refractory advanced pancreatic cancer.[1,13]

Several phase II trials have investigated the safety and efficacy of second line chemotherapy and showed that numerous patients do respond to salvage chemotherapy.[14] However, these studies did not provide a significantly detailed analysis of clinical factors that may present as prognostic value for patients after the failure of first line chemotherapy.[15,16]

Marechal et al[17] reported that performance status and albumin level were independent prognostic factors in chemotherapy naive and gemcitabine refractory patients with advanced pancreatic cancer. Poor performance status and a low albumin level may reflect the increased disease burden status and the inability to complete the prescribed treatment due to the aggressive matter of pancreatic cancer. In a phase II trial of second line treatment with oxaliplatin, 5-FU and folinic acid in advanced pancreatic cancer after pre-treatment with gemcitabine, patients who had responded to first-line gemcitabine were found to be more likely to respond or stabilize their disease with second line chemotherapy.[18]

Fornaro et al.[19] presented a multivariate prognostic model for second line chemotherapy in advanced pancreatic cancer and biliary cancer. Their data highlights that performance status, CA 19-9 and duration of first line chemotherapy are very reliable clinical parameters to estimate prognosis in pancreas cancer and biliary cancer.

Sinn et al[7] established a multivariate prognostic model for second line chemotherapy in metastatic pancreatic cancer. Three factors significantly influenced the second line associated overall survival: Karnofsky Performance

Status, CA19-9 measured at initiation of second line chemotherapy and duration of first line chemotherapy. Moreover, other previous studies revealed that poor general condition and highly elevated tumor marker CA 19-9 are unfavorable factors to prognosis and may strongly influence the overall survival after the initiation of second line chemotherapy.[20]

Our analysis was to evaluate how many patients in the palliative treatment course proceed with SL therapy in actual clinical practice and what are the typical characteristics of these SL patients. From the results, our goal was to establish a simplified prognostic model that could clinically predict which patients may receive the maximum benefit of SL treatment.

Compared to other previous prognostic scoring systems established with significant variables from the final multivariate analysis, we made our nomogram scoring system with variables from comparing two groups classified by the length of OS2: 6months below and 6 months above, considering the rapid progression and short survival after the progression under first line chemotherapy.[21] However, the significant variables from the previous analysis did not differ greatly compared to the multivariate analysis from the same set of development cohort group.

Despite the Harrell's S-index and iAUC internal validation index of the nomogram, this scoring system allows reliable differentiation into 3 prognostic groups (good, intermediate, poor) which demonstrate clear differences in OS2. Patients in the poor prognosis group had a median OS2 of about 12 weeks, and those in the good prognosis group of about 28 weeks, demonstrating a difference of about 16 months. Based on our prognostic nomogram and the validation, the possibility that second line chemotherapy can provide any benefit for these patients cannot be warranted. However, second line chemotherapy could be beneficial to patients if decision of the treatment is carefully considered in these patients regarding the prognosis afterwards with significant predictive clinical parameters.

Our results highlight remarkable heterogeneity in survival of patients with advanced pancreatic cancer who receive second line chemotherapy, and our prognostic nomogram may help for patient selection of second line chemotherapy. Despite the fact that pragmatic parameters are already frequently used in decision making for the initiation of second line chemotherapy, our final nomogram presents simplicity compared to previous approach with many variables in the scoring system. In addition to strengthening decision-making for clinicians, these tools may be beneficial for selection of patients for treatment, stratified random assignment to ensure well balanced treatment groups, and for a potential optimization of clinical trial model. Moreover, with the prognostic monogram, the development of risk adapted strategies for pancreatic cancer in palliative second line management could be also considered in the different risk groups identified by the score.

There are several points which provide differentiation among other similar studies. The inclusion period in our study was long enough, from 2010 to 2015, to include sensational regimens introduced in the field. This time period is very important in the era of pancreatic cancer since clinical practices have changed with the approval of the FOLFIRINOX and gemcitabine plus nab-paclitaxel chemotherapy.[22] Our study evaluated a large cohort population including patients treated with FOLFIRINOX regimen in second line chemotherapy, which was approved in 2011 and widely available from 2014.[23] Parameters used in the model are clinically approached, simple to collect for clinicians, and consistent with previous models devised. Internal validation was demonstrated to prove the satisfactory performance and validity of the nomogram. Our prognostic nomogram was externally validated through patient group in 2016 of Yonsei University Hospital. Therefore, our final prognostic nomogram made an attempt to confirm the reliability in the era of new, highly efficient treatment regimens for advanced pancreatic cancer. Few similar prognostic models suggested currently have limitation of heterogeneity in first line chemotherapy

treatments. However, our study made assess to similar prognostic factors in homogenous gemcitabine based first line chemotherapy patient groups.[24]

However, there are limitations in generalizing the prognostic nomogram due to the retrospective feature of the study. According to the slightly low C-index of the nomogram, the predictive ability of the scoring system is not fully qualified to be used in general practice yet. Moreover, the external validation also showed low predictive ability. Hopefully, with the significant variables from the analysis, the predictive ability will improve with more data sets. External validation in different hospitals and in other countries will definitively confirm the worldwide relevance of the model in the future. Thus, the prognostic usefulness of our nomogram needs to be confirmed through a large prospective validation in the future. Furthermore, there were high rate of missing data collection, particularly albumin, C-reactive protein levels, LDH levels mentioned in other similar studies to propose other specific clinical parameter in the prognostic monogram.

V. CONCLUSION

Many oncologic approaches are currently made to figure out which patients truly benefit from receiving second line chemotherapy on molecular basis but little is being researched on clinical basis.[25] There is no worldwide reliable clinical parameter scoring system available to support the physician's decision to go on with second line therapy or give up salvage chemotherapy and progress to best supportive care.[24]

Our study identified prognostic factors influencing the survival of advanced pancreatic cancer patients after the progression of first line chemotherapy. The significant factors depending on the OS2 were peritoneum metastasis, number of metastatic lesion, CA19-9 level and thrombotic event. With the significant prognostic factors of OS2, we ultimately devised a prognostic nomogram for practical use in clinical field. Despite the limitations mentioned above, this

prognostic scoring system may help to develop strategies to identify patients who can obtain real benefit from second line chemotherapy.

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ABSTRACT(IN KOREAN)

초치료에 실패한 전이성 췌장암의 2차 전신 항암치료 효과에 미치는 임상적 예측인자 분석

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배경 및 목적

췌장암에서 일차 항암 요법 치료 실패 시 이차 항암 요법 시도의 생존 이득에 해서는 아직 확립된 바가 없다. 본 연구에서는 일차 항암 치료 실패 후 생존에 영향을 끼치는 예후 인자들을 분석하여 궁극적으로 임상적인 예후 인자들로 이차 항암 치료와 보존적 치료를 결정하는데 도움을 주는 예측 모델을 만들고자 하였다.

대상 및 방법

2010년 1월부터 2015년 12월까지 연세대학교 병원에서 췌장암을 진단받은 환자 중 gemcitabine을 포함한 일차 항암 치료를 진행한 501명을 대상으로 하였으며, 이후 일차 항암 치료 실패 후 이차 항암 치료를 진행한 최종 245을 대상으로 후향적으로 분석하였다. 이 중 일차 항암 치료 실패 후부터 사망까지의 기간을 6개월 미만과 이상, 두 그룹으로 나누어 대상 환자의 임상적 특징과 생존율 등을 조사하여 비교하였다. 4가지 임상 요인들이 일차 항암 치료 실패 후부터의 생존기간에 통계학적으로 유의한 영향을 주었다; 복막 전이($p<0.001$), 전이 병변의 개수($p<0.001$), 혈전의 유무($p=0.003$) 그리고 CA 19−9 수치($p=0.011$). 유의한 변수들로 도출한 예후 예측 모델의 Harrall's C−index 예측값은 0.62로, 도출된 예후 예측 인자들로 노모그램을 만들어 이차 항암 치료의 이득을 예측하고자 하였다.

결과

4 가지 임상 요인들이 일차 항암 치료 실패 후부터의 생존기간에 통계학적으로 유의한 영향을 주었다; 복막 전이($p<0.001$), 전이 병변의 개수($p<0.001$), 혈전의 유무($p=0.003$) 그리고 CA 19-9 수치($p=0.011$). 유의한 변수들로 도출한 예후 예측 모델의 Harrall's C-index 예측값은 0.62 로, 도출된 예후 예측 인자들로 노모그램을 만들어 이차 항암 치료의 이득을 예측하고자 하였다.

결론

복막 전이, 혈전의 발생, 두 곳 이상의 전이 병변 그리고 CA19-9 90m/UL 상에서는 일차 항암 치료 실패 이후 불량한 예후를 시사한다. 도출된 예후 예측 노모그램은 임상의 들에게 일차 항암 치료 실패 후 이차 항암 치료를 결정하는 데 도움을 줄 수 있을 것이다.

핵심되는 말 : 췌장암, 2차항암요법, 예후 예측 모델