<붙임 4>

기관고유연구사업 결과 보고

결 재	과제책임자	과 장	부 장

※ 협조 :

- 사업단 소속 연구직의 경우 국가암관리사업단장
- 연구(의사직), 의사직, 의학물리학직의 경우 소속 센터장

본인이 수행한 2008~2010년도 기관고유연구사업 과제 연구결과를 붙임과 같이 보고합니다.

과제명	폐암환자에서 맞춤 항암치료법 개발을 위한 약물유전체 연구 (Whole Genome-wide Pharmacogenomic Study for Personalized Chemotherapy in Lung Cancer)
과제책임자 (소속, 성명)	폐암연구과 한 지 연
총연구비	360,000천원 (2008년:120,000천원,2009년:120,000천원,2010년:120,000천원)
총연구기간	2008년1월1일 ~ 2010년12월30일

붙임 : 기관고유연구사업 최종보고서 1부

2010년 12월 30일

기관고유연구사업 최종보고서

편집순서 1 : 겉표지 (앞면)

(과제번호 : 0810130)

연구과제명 (국문)

폐암환자에서 맞춤 항암치료법 개발을 위한 약물유전체 연구

연구과제명 (영문)

Whole Genome-wide Pharmacogenomic Study for Personalized Chemotherapy in Lung Cancer

과제책임자 : 한 지 연

국 립 암 센 터

편집순서 1 : 겉표지 (측면, 뒷면)

(뒷면) (측면)

1. 이 보고서는 국립암센터 기관고유연구사업 최종보고서입니다.

2. 이 보고서 내용을 인용할 때에는 반드시 국립암센터 연구사업 결과임을 밝혀야 합니다.

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편집순서 2 : 제출문

제 출 문

국립암센터 원장 귀하

이 보고서를 기관고유연구사업 “ 폐암환자에서 맞춤 항암치료법 개발을 위한 약물 유전체 연구” 과제의 최종보고서로 제출합니다.

2010. 12 . 30

국 립 암 센 터

과 제 책 임 자 : 한 지 연

편집순서 3 : 목차

목 차

※ 여러개의 세부과제로 과제가 구성된 경우 위 목차와 동일하게 세부과제별로 작성함

(I. 총괄과제, II. 제1세부과제, III. 제2세부과제.....)

편집순서 4 : 요약문 (한글)

< 요 약 문 >

연구분야(코드)	B-2		과제번호	0810130
과 제 명	폐암환자에서 맞춤 항암치료법 개발을 위한 약물유전체 연구			
연구기간/연구비 (천원)	합계	2008년 1월1일 ~ 2010년12월31일		360,000
	1차년도	2008년1월1일 ~2008년12월31일		120,000
	2차년도	2009년1월1일 ~2009년12월31일		120,000
	3차년도	2010년1월1일 ~2010년12월31일		120,000
과제책임자	성 명	한지연	주민등록번호	
	전화번호	031-920-1154	전 자 우 편	jymama@ncc.re.kr
색인단어	국문	폐암, 약물유전체 분석		
	영문	lung cancer, pharmacogenomics		

◆ 연구목표

<최종목표>

- 폐암환자의 유전체 다양성 분석을 통한 한국 폐암 환자의 약물유전체 모델 확립
- 약물유전체 분석에 기초한 개별 맞춤 항암치료법 개발
  - 항암 효과 극대화 (best tumor response)
  - 독성 최소화 (Least toxicity)

<당해년도 목표>

- GWAS (genome-wide association study)를 통한 한국폐암 환자의 특이적 유전체 다형성 모델 확립
- 폐암 환자의 맞춤 항암치료를 위한 약물유전체 모델 확립

◆ 연구내용 및 방법

○ Whole genome-based SNP analysis 를 통한 한국 폐암의 새로운 SNP을 발굴 및 폐암환자 에서의 임상적 의의 분석

- irinotecan+cisplatin 요법을 이용한 임상시험에 참여한 폐암환자의 말초혈액에서 DNA를 분리하여 Affymetrix® Genome-Wide Human SNP 5.0 chip을 이용하여 분석함.
- 임상적으로 중요한 rinotecan 관련 심한 독성으로 Grade 3 설사 및 grade 4 백혈구감소증이 발생과 관련된 SNP 분석
- 항암치료의 반응과 관련된 SNP 분석
- 환자의 생존률과 관련된 SNP 분석

○ Cisplatin 내성형 모델 확립을 위한 임상시험의 진행 및 약물유전체연구 실시

- 진행성 비소세포폐암환자로부터 폐암조직을 획득하여 ERCC1 발현을 관찰하고, 발현 정도에 따른 치료 성적 및 예후를 비교 관찰하기 위한 무작위 제2상 임상시험을 계속 진행 중임.
  - 연구제목: Randomized phase II study of irinotecan/cisplatin versus gemcitabine/cisplatin as the first-line therapy for patients with advanced non-small cell lung cancer (NSCLC); pharmacogenomic study for providing personalized strategy to the treatment of advanced NSCLC
  - 임상시험 IRB 승인일: 2009년 2월 5일
  - 임상시험 시작일: 2009년 2월 20일
  - 현재 (2010년 11월 30일) 까지 환자 등록 사항:
    127명 연구등록함/총 284명 등록 예정

○ 임상시험에 참여하는 환자의 폐암조직과 혈장을 수집하여 항암제의 대사 및 작용표적에 관련된 대상 유전자의 발현 및 변이 비교 분석하고, 향후 폐암조직 대신 혈장 DNA로 대치될 가능성 평가함.

Randomized phase II study of gefitinib versus gefitinib plus simvastatin study 에 참여한 환자들의 종양조직과 혈장DNA를 이용하여 gefitinib 치료의 최상의 predictive marker 인 EGFR mutation 분석을 실시함

종양조직: 18 샘플

PCR-based direct sequencing을 실시하여 EGFR exon 18-21까지의 변이를 분석함

혈장DNA: 91 샘플

peptide nucleic acid (PNA) clamping - based asymmetric PCR with melting curve analysis 실시함

15 개의 paired 샘플 분석: 73% concordant rate 확임함.

◆ 연구성과

-정량적 성과

구분	달성치/목표치[1)]	달성도(%)
SCI 논문 편수	18/9	200
IF 합	82.599/34	243
기타 성과		

1) 총연구기간내 목표 연구성과로 기 제출한 값

-정성적 성과

·

◆ 참여연구원 (최종연도 참여인원)	성 명	이종은, 신은순, 조은영, 김진영, 유남진, 윤성진
	주민등록번호	******-*******, ******-*******, ******-*******, ******-*******

편집순서 5 : 요약문 (영문)

Project Summary

Title of Project	Whole Genome-wide Pharmacogenomic Study for Personalized Chemotherapy in Lung Cancer
Key Words	lung cancer, pharmacogenomics
Project Leader	JI-YOUN HAN, M.D., Ph.D.
Associated Company	

Irinotecan is characterized by a wide interpatient variability in pharmacokinetics and subsequent pharmacologic effects and toxicity. In addition, its pharmacology is complex and may be dependent on the interplay of metabolizing enzymes and transporters. Therefore, metabolizing enzymes, transporters, and other potential regulatory factors should be viewed and evaluated as an integrated system rather than single component for the accurate prediction of irinotecan-PK and toxicity. To define an integrated pharmacogenetic model for predicting irinotecan pharmacokinetic and severe toxicity, we evaluated multivariate analysis using 15 polymorphisms within seven genes with putative influence on metabolism and transport of irinotecan. A total of 107 NSCLC patients treated with irinotecan were evaluated for PK and genotyped for the UGT1A1 *6, UGT1A1*28, UGT1A9*22, ABCB11236C>T, 2677G>T/A, 3435C>T, ABCC2-24C>T, 1249G>A, 3972C>T, ABCG234G>A, 421C>A, and SLCO1B1 - 11187G>A, 388A>G, and 521T>C, and CYP3A5*3 polymorphisms. Multivariate linear and logistic regression analyses including genotypes and clinicopathologic factors were performed. SN-38 AUC was significantly correlated with ANCs (r=-0.3, p=0.009) and grade 4 neutropenia (p=0.01). The UGT1A1*6/*6, UGT1A9*1/*1 or *1/*22, and SLCO1B1521TC or CC genotypes, and female-gender were predictive for higher AUCSN-38 in multivariate analysis. Among them, SLCO1B1521TC or CC and UGT1A1*6/*6 genotypes were independently predictive for grade 4 neutropenia in multivariate analysis (OR=3.8 and 7.4, respectively). Although no significant association was observed between PK parameters and grade 3 diarrhea, UGT1A9*1/*1, ABCC23972CC, and ABCG234GA or AA genotypes were independently predictive for grade 3 diarrhea in multivariate analysis (OR=6.3, 5.6, and 5.1, respectively). Patient selection based on integrated pharmacogenetic model would be helpful for predicting irinotecan-PK and severe toxicities in NSCLC patients. However, cancer is a complex disorder caused by multiple genetic factors and the understating of the precise role of all participating factors is still limited. Therefore, more sophisticated approaches such as genome-wide linkage analysis and integrate drug pathway profiling may be needed to develop an improved genetic-based therapeutic strategy for NSCLC patients treated with irinotecan.

편집순서 6 : 연구결과

1. 연구의 최종목표

- 폐암환자의 유전체 다양성 분석을 통한 한국 폐암 환자의 약물유전체 모델 확립
- 약물유전체 분석에 기초한 개별 맞춤 항암치료법 개발
  - 항암 효과 극대화 (best tumor response)
  - 독성 최소화 (Least toxicity)

2. 연구의 내용 및 결과

(가) Whole genome-based SNP analysis 를 통한 한국 폐암의 새로운 SNP을 발굴 및 임상적 의의 분석

- 2002-2006년 사이 국립암센터에서 실시된 전향적 임상시험에 참여한 폐암 환자 (비소세폐암 124명, 소세포폐암 145명)의 말초혈액에서 DNA를 분리함.
- Affymetrix Genome-wide human SNP 5.0 chip을 이용하여 유전체 다형성 분석을 실시함.
- GWAS data QC process

  각 SNP에 대해 Hardy-Weinberg Equilibrium test, Marker Call Cut-off, MAF Cut-off를 적용하였고, 유의 SNP으로 선정된 것의 경우는 signal intensity cluster의image를 확인하여 assay의 정확도를 검증함.

NSCLC	case	control	missing	SNPs
grade 3 diarrhea	11	91	20	249771
grade 4 neutropenia	24	78	20	249771
partial response	56	42	24	249771
progression-free survival	95	3	24	249771
overall survival	95	0	27	249771
SCLC				
grade 3 diarrhea	18	121	0	421422
grade 4 neutropenia	29	110	0	421422
disease progression	19	108	12	421422
progression-free survival	121	11	7	421422
overall survival	118	0	21	421422

*** 질환별 별첨 보고 내용 참조

(나) Cisplatin & Gemcitabine resistance phenotype 분석

Purpose: To investigate whether polymorphisms in DNA repair genes affect clinical outcome of never-smokers with lung adenocarcinoma (NSLA).

Experimental design: Common polymorphisms in *RRM1*,*ERCC1*,and *XRCC1* were genotyped onDNA from158patients among 313 NSLA who were randomized to receive gefitinib or gemcitabine and cisplatin (GP) as first-line therapy. Immunohistochemistry for ERCC1 (n=38) and direct sequencing of *EGFR*(n=42)wereperformedusingtumorsamples.

Results: Patients with *XRCC1*399Arg/Arg showed higher responserate(RR) to gefitinib (71%v36%,P=0.002) and had more *EGFR*-mutant tumors (82%v29%,P=0.001) than those with Gln allele. Patients with *ERCC1*8092AA showed higher RR to GP than CC or CA genotypes (100%v44%,P=0.043).Whencomparinggefitinibversus GP,patientswith*XRCC1*399Arg/Arg(7.5v6.6months[M],P=0.013),*RRM1*2464GG (11.5v6.0M,P=0.004), and *ERCC1*8092CA (7.5v6.4M,P=0.024)showedsignificantlylongerprogression-free survival (PFS) with gefitinib. When these three genotypes were analyzed jointly, patients harboring more than two showed significantly longer PFS with gefitinib (8.1v6.4M, P=0.009).Whereas, patients without these genotypes showed a trend toward longer PFS with GP (6.3v2.0M, P=0.06). In a multivariate Cox regression model, greater number of specific genotypes independently predicted improved overallsurviva l(HR=0.5;95%CI,0.3-0.8;P=0.006).

Conclusions: Patients with *XRCC1*399Arg/Arg, *RRM1*2464GG, and *ERCC1*8092CA genotypes did benefit from gefitinib. The greater number of these genotypes may predict favorable prognosis for NSLA.

Table 1. Patients' characteristics (n=158)

	GP (n=77)		Gefitinib (n=81)		
	N	(%)	N	(%)	P
Age, years					
Median (Range)	56 (19-71)		57 (32-74)		
Sex					1.0
Male	7	(9)	7	(9)	
Female	70	(91)	74	(91)	
Stage					1.0
IIIB	7	(9)	7	(9)	
IV	70	(91)	74	(91)	
Performance status (ECOG)					.747
0	26	(34)	24	(30)	
1	41	(53)	48	(59)	
2	10	(13)	9	(11)	
Second-line therapy					
Platinum-based regimen	0	(0)	54	(81)	
EGFR-TKIs	60	(81)	0	(0)	
Non-platinum regimen	14	(19)	13	(19)	
RRM1 2455A>G (rs3177016)					
AA	24	(31)	27	(34)	.846
AG	40	(52)	42	(52)	
GG	13	(17)	11	(14)	
RRM1 2464G>A (rs1042858)					
GG	7	(9)	8	(10)	.966
GA	28	(36)	28	(35)	
AA	42	(55)	45	(56)	
RRM1 -524C>T (rs11030918)					
CC	3	(4)	8	(10)	.323
CT	28	(36)	26	(32)	
TT	46	(60)	47	(58)	
RRM1 -37C>A (rs12806698)					
CC	46	(60	48	(59)	.446
CA	28	(36)	26	(32)	
AA	3	(4)	7	(9)	
ERCC1 8092C>A (rs3212986)					
CC	38	(49)	34	(42)	.434
CA	35	(46)	39	(48)	

AA	4	(5)	8	(10)	
ERCC1 118C>T (rs11615)					
CC	49	(64)	50	(62)	.679
TC	21	(27)	26	(32)	
TT	7	(9)	5	(6)	
XRCC1 Arg399Gln (rs25487)					
Arg/Arg	42	(55)	45	(56)	.086
Arg/Gln	34	(44)	29	(36)	
Gln/Gln	1	(1)	7	(9)	
ERCC1 expression (n=38)					
Positive	8	(57)	13	(54)	.859
Negative	6	(43)	11	(46)	
EGFR mutations (n=42)					
Positive	8	(44)	15	(63)	.245
Negative	10	(56)	9	(38)	

Table 2. Response rate by treatment assignment within genotypes, ERCC1 expression, and EGFR mutations

	GP			Gefitinib			
	PR (%)	SD+PD (%)	*P*	PR (%)	SD+PD (%)	*P*	*P* (GP vs. Gefitinib)
RRM1 2455A>G							
AA	14 (61)	9 (31)	.232	18 (67)	9 (33)	.393	.670
AG	15 (39)	24 (62)		21 (50)	21 (50)		.296
GG	6 (46)	7 (54)		6 (55)	5 (46)		1.0
RRM1 2464G>A							
GG	2 (29)	5 (71)	.296	7 (88)	1 (13)	.154	.041
GA	15 (58)	11 (42)		14 (50)	14 (50)		.571
AA	18 (43)	24 (57)		24 (53)	21 (47)		.328
RRM1 -524C>T							
CC	1 (33)	2 (67)	.888	5 (63)	3 (38)	.760	.545
CT	13 (48)	14 (52)		13 (50)	13 (50)		.893
TT	21 (47)	24 (53)		27 (57)	20 (43)		.301
RRM1 -37C>A							
CC	21 (47)	24 (53)	.592	27 (56)	21 (44)	.592	.355
CA	13 (48)	14 (52)		13 (50)	13 (50)		.893
AA	1 (33)	2 (67)		5 (71)	2 (29)		.500
ERCC1 8092C>A							
CC	17 (46)	20 (54)	.082	17 (50)	17 (50)	.268	.733
CA	14 (41)	20 (59)	(.043*)	25 (64)	14 (36)	(.456*)	.050
AA	4 (100)	0 (0)		3 (38)	5 (63)		.081
ERCC1 118C>T							
CC	25 (52)	23 (48)	.351	27 (54)	23 (46)	.934	1.0

TC	7 (33)	14 (67)		15 (58)	11 (42)		.096
TT	3 (50)	3 (50)		3 (60)	2 (40)		.849
XRCC1 Arg399Gln							
Arg/Arg	22 (54)	19 (46)	.304	32 (71)	13 (29)	.006	.094
Arg/Gln	13 (39)	20 (61)	(.183[+])	10 (35)	19 (66)	(.002[+])	.690
Gln/Gln	0 (0)	1 (100)		3 (43)	4 (57)		1.0
ERCC1 expression							
Negative	5 (83)	1 (17)	.026	6 (55)	5 (46)	1.0	.333
Positive	1 (13)	7 (88)		7 (54)	6 (46)		.085
EGFR mutations							
Positive	3 (38)	5 (63)	1.0	13 (87)	2 (13)	<.0001	.026
Negative	4 (40)	6 (60)		1 (11)	8 (89)		.303

GP, gemcitabine and cisplatin; PR, partial response; SD, stable disease; PD, progressive disease by RECIST.

**ERCC1*8092CC+CAvAA

[+]*XRCC1* 399 Arg/Arg v Arg/Gln+Gln/Gln

Table 3. Association of genotypes with ERCC1 expression or EGFR mutations

			ERCC1 expression (n=38)			*EGFR* mutations (n=42)		
			Negative, N (%)	Positive, N (%)	P	Negative, N (%)	Positive, N (%)	P
RRM1	2455A>G	AA	8 (73)	3 (27)	.056	9 (69)	4 (31)	.112
		AG	6 (29)	15 (71)		8 (35)	15 (65)	
		GG	3 (50)	3 (50)		2 (33)	4 (67)	
RRM1	2464G>A	GG	3 (75)	1 (25)	.393	2 (50)	2 (50)	.866
		GA	6 (46)	7 (54)		7 (50)	7 (50)	
		AA	8 (38)	13 (62)		10 (42)	14 (58)	
RRM1	-524C>T	CC	2 (100)	0 (0)	.140	3 (75)	1 (25)	.346
		CT	3 (27)	8 (73)		4 (33)	8 (67)	
		TT	12 (48)	13 (52)		12 (46)	14 (54)	
RRM1	***-37C>A***	CC	12 (48)	13 (52)	.140	12 (46)	14 (54)	.346
		CA	3 (27)	8 (73)		4 (33)	8 (67)	
		AA	2 (100)	0 (0)		3 (75)	1 (25)	
ERCC1	8092C>A	CC	9 (64)	5 (36)	.110	8 (50)	8 (50)	.841
		CA	8 (36)	14 (64)		10 (44)	13 (56)	
		AA	0 (0)	2 (100)		1 (33)	2 (67)	
ERCC1	***118C>T***	CC	12 (52)	11 (48)	.410	11 (42)	15 (58)	.280
		TC	5 (36)	9 (64)		8 (57)	6 (43)	
		TT	0 (0)	1 (100)		0 (0)	2 (100)	
XRCC1	Arg399Gln	Arg/Arg	9 (50)	9 (50)	.746	4 (18)	18 (82)	.001
		Arg/Gln	6 (38)	10 (63)		12 (71)	5 (29)	
		Gln/Gln	2 (50)	2 (50)		3 (100)	0 (0)	

Table 4. Median progression-free survival by treatment assignment within genotypes, ERCC1 expression, and *EGFR*mutations

	GP			Gefitinib			
	No	mo (95% CI)	*P*	No	mo (95% CI)	*P*	*P* (GP v Gefitinib)
RRM1 2455A>G							
AA	23	8.0 (4.9-11.1)	.632	27	6.4 (4.5-8.3)	.970	.184
AG	40	6.5 (5.6-7.4)		42	4.1 (0.1-9.3)		.102
GG	13	5.9 (4.4-7.4)		11	4.3 (1.4-7.2)		.873
RRM1 2464G>A							
GG	7	6.0 (0.1 -16.8)	.851	8	11.5 (6.5-16.5)	.212	.004
GA	27	7.0 (5.5-8.5)		28	4.3 (0.2-8.6)	(.089)†	.380
AA	42	6.3 (5.6-7.0)		45	4.1 (2.8-5.4)		.690
RRM1 -524C>T							
CC	3	9.1 (0-20.5)	.581	8	3.0 (0.1-7.0)	.867	.581
CT	27	6.9 (4.5-9.3)		26	4.1 (0.2-9.1)		.426
TT	46	6.3 (5.7-6.9)		47	6.4 (2.9-9.9)		.051
RRM1 -37C>A							
CC	46	6.3 (5.7-6.9)	.581	48	5.9 (3.1-8.7)	.962	.065
CA	27	6.9 (4.5-9.3)		26	4.1 (0.3-9.1)		.434
AA	3	9.1 (0-20.5)		7	5.0 (0.1-11.2)		.644
ERCC1 8092C>A							
CC	37	6.3 (5.5-7.1)	.586	34	3.6 (1.7-5.5)	.068	.634
CA	35	6.4 (5.2-7.6)		39	7.5 (5.7-9.3)	(.022)‡	.024
AA	4	7.5 (5.5-9.5)		8	2.1 (0.1-9.2)		.643
ERCC1 118C>T							

CC	49	6.4 (5.3-7.7)	.941	50	5.9 (3.2-8.6)	.796	.510
TC	21	6.6 (6.2-7.0)		26	4.1 (0.9-7.3)		.329
TT	6	5.3 (2.8-7.8)		5	8.8 (0.1-19.8)		.205
XRCC1 Arg399Gln							
Arg/Arg	41	6.6 (6.2-7.0)	<.0001	45	7.5 (5.6-9.4)	.034	.013
Arg/Gln	34	6.3 (4.9-7.7)	(.714) #	29	2.1 (1.2-3.0)	(.009)#	.617
Gln/Gln	1	1.1		7	2.6 (1.1-4.1)		.353
ERCC1 expression							
Positive	8	5.9 (3.3-8.5)	.955	13	7.5 (1.4-13.6)	.806	.451
Negative	6	5.1 (0.4-9.8)		11	5.9 (1.7-10.1)		.678
EGFR mutations							
Positive	8	5.1 (1.8-8.4)	.542	15	8.0 (6.4-9.6)	.014	.155
Negative	10	5.9 (2.3-9.5)		9	1.9 (0.4-3.4)		.863
No of specific genotypes*							
0	15	6.3 (4.8-7.8)	.849	19	2.0 (1.9-2.1)	<.0001	.063
1	41	6.5 (5.3-7.7)		35	5.9 (2.8-9.0)		.194
2 or 3	21	6.4 (5.5-7.3)		27	8.1 (6.6-9.6)		.009

GP, gemcitabine and cisplatin; mo, months.

†*RRM1*2464GGvGA+AA;‡*ERCC1*8092CAvCC+AA;#*XRCC1* 399 Arg/Arg v Arg/Gln+Gln/Gln

**RRM1*2464GG,*ERCC1*8092CA,and*XRCC1*399Arg/Arg

Fig. 1

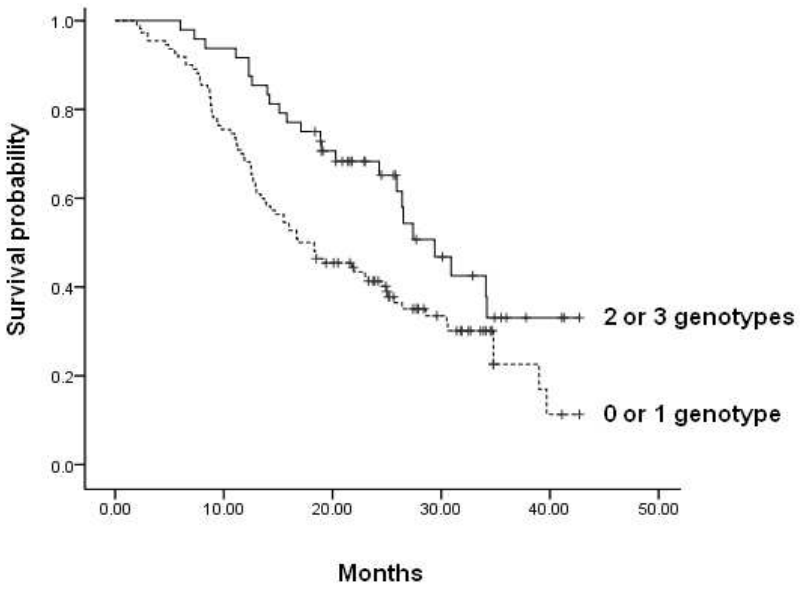

Figure 1. Kaplan-Meier curve for overall survival in relation to number of specific genotypes** *RRM1* 2464GG, *ERCC1* 8092CA, or *XRCC1* 399 Arg/Arg

다) Comparison of EGFR mutations between tumor cells and plasma DNA from NSCLC patients

Detection of EGFR mutations

Whole-blood and tissue samples were collected immediately before treatment. Plasma was separated within 2 hr after the sample collection and stored at -80℃ until used. Genomic DNA was extracted from plasma and paraffin-embedded tissues by using the QIAamp DNA mini kit (Qiagen, CA). We used peptide nucleic acid (PNA) clamping‐based asymmetric PCR with melting curve analysis using unlabeled probes.25 A capillary PCR machine (Roche, Light Cycler, USA) was used instead of plate PCR, and the melting carve analysis for the probe peak was done in the same machine. Forward and reverse primers were designed to amplify the commonly mutated portions of exon fragments 19 and 21, and the amplicon sizes were 91 and 89 base pairs, respectively. Locked nucleic acids were incorporated into the forward primer of exon 19 to increase the annealing temperature. The forward primer for exon 19 antisense PNAs and sense mutation probes were designed to span the mutation sites of exons 19 and 21 of the EGFR gene. The antisense PNA complementary to the wild-type sequence was used to clamp PCR for wild-type but not mutant alleles. The sense mutation probes that were complementary to mutant alleles were used to detect both wild-type and mutant alleles. The mutation probe for exon 19 was complementary to E746-A750del type 1 (2235-2249del) and was used to detect wild-type and E746-A750del type 2 (2236-2250del) mutant as well as E746-A750del type 1. The mutation probe for exon 21 is complementary to L858R (T2573G) and was used to detect both wild-type and L858R mutant alleles.

Comparison of EGFR mutations between tumor cells and plasm DNA

Among a total of 106 patients, 94 plasma DNA samples were adequate for EGFR mutation analysis. Activating mutations were detected in 26 of 94 (28%) cases (23 exon 19 deletions and 3 exon 21 L858R mutations, Table 1). To validate the plasma EGFR mutation results, we tested the two major EGFR mutations, the exon 19 deletion and exon 21 (L858R), in the paired tumor tissues. In the 15 paired specimens of plasma and tumor tissues, 11 (73%) revealed concordant results. The comparison between EGFR mutation status in plasma and tumor samples is summarized in Table 4. Although they were not statistically significant, trends toward higher frequency of EGFR mutations were observed in adenocarcinoma (32% [23/71] vs. 13% [3/23] for non-adenocarcinoma, P=0.107), women (36% [16/45] vs. 20% [10/49] for men, P=0.101), and never smokers (33% [15/46] vs. 23% [11/48] for ever smokers, P=0.294). Among the entire population, patients with EGFR-mutant tumors showed significantly higher response rates (69% [18/26] vs. 21% [14/68] for wild-type EGFR, P<0.0001), and longer PFS (HR=0.386 [95% CI, 0.238-0.627], P<0.0001) and OS (HR=0.540 [95% CI, 0.316-922], P=0.024) compared to those with wild-type EGFR tumors.

3. 연구결과 고찰 및 결론

1) irinotecan pharmacogeneticsin Korean lung cancer patients

Irinotecan is characterized by a wide interpatient variability in pharmacokinetics and subsequent pharmacologic effects and toxicity. In addition, its pharmacology is complex and may be dependent on the interplay of metabolizing enzymes and transporters. Therefore, metabolizing enzymes, transporters, and other potential regulatory factors should be viewed and evaluated as an integrated system rather than single component for the accurate prediction of irinotecan-PK and toxicity. To define an integrated pharmacogenetic model for predicting irinotecan pharmacokinetic and severe toxicity, we evaluated multivariate analysis using 15 polymorphisms within seven genes with putative influence on metabolism and transport of irinotecan. A total of 107 NSCLC patients treated with irinotecan were evaluated for PK and genotyped for the UGT1A1 *6, UGT1A1*28, UGT1A9*22, ABCB11236C>T, 2677G>T/A, 3435C>T, ABCC2-24C>T, 1249G>A, 3972C>T, ABCG234G>A, 421C>A, and SLCO1B1‐11187G>A, 388A>G, and 521T>C, and CYP3A5*3 polymorphisms. Multivariate linear and logistic regression analyses including genotypes and clinicopathologic factors were performed. SN-38 AUC was significantly correlated with ANCs (r=-0.3, p=0.009) and grade 4 neutropenia (p=0.01). The UGT1A1*6/*6, UGT1A9*1/*1 or *1/*22, and SLCO1B1521TC or CC genotypes, and female-gender were predictive for higher AUCSN-38 in multivariate analysis. Among them, SLCO1B1521TC or CC and UGT1A1*6/*6 genotypes were independently predictive for grade 4 neutropenia in multivariate analysis (OR=3.8 and 7.4, respectively). Although no significant association was observed between PK parameters and grade 3 diarrhea, UGT1A9*1/*1, ABCC23972CC, and ABCG234GA or AA genotypes were independently predictive for grade 3 diarrhea in multivariate analysis (OR=6.3, 5.6, and 5.1, respectively). Patient selection based on integrated pharmacogenetic model would be helpful for predicting irinotecan-PK and severe toxicities in NSCLC patients. However, cancer is a complex disorder caused by multiple genetic factors and the understating of the precise role of all participating factors is still limited. Therefore, more sophisticated approaches such as genome-wide linkage analysis and integrate drug pathway profiling may be needed to develop an improved genetic-based therapeutic strategy for NSCLC patients treated with irinotecan.

2) DNA repair gene polymorphisms and benefit from gefitinib in never-smokers with lung adenocarcinoma

In this report, we examined the relationship between seven SNPs in DNA repair genes and clinical outcome of NSLA who were treated with gefitinib or GP as first-line therapy. We found treatment-related differences in PFS and RR within those SNPs. Among patients with XRCC1 399Arg/Arg, RRM1 2464GG, and ERCC1 8092CA genotypes, significantly longer PFS was observed with gefitinib. These genotypes also showed a trend toward higher RR

to gefitinib. Moreover, patients harboring more than two specific genotypes showed significantly longer PFS with gefitinib. Conversely, patients without any of them showed a trend toward longer PFS with GP. We also noted that the greater number of specific genotypes independently predicted better prognosis in NSLA. Although single gene effect was minimal, the joint analysis of multiples SNPs showed a significant effect on survival. These results support the substantial evidence of cumulative influence by multiple favorable variants for predicting clinical outcome in lung cancer patients.

The lower DRC has been associated with higher lung cancer risk in never-smokers. The XRCC1 399Gln variant allele is less likely to repair DNA damages and has been associated with higher risk of lung cancer in never-smokers but lower risk in heavier smokers.23, 24 Recently one study with 122 healthy Japanese workers found that individuals with Gln allele had significantly higher DNA adducts in lymphocytes in never-or former smokers but not in current-smokers.28 In our study, the XRCC1 399Arg/Arg genotype, which is associated with intact DRC, showed favorable response and PFS benefit from gefitinib. Moreover, this genotype was significantly associated with sensitive EGFR mutations. These findings suggest that never-smokers harboring Arg/Arg genotype that is related with intact DRC seem to have a relatively homogenous lung tumor that is characterized by somatic mutations of EGFR gene rather than accumulating multiple genetic and epigenetic alterations, which may lead to higher response to gefitinib and improved survival.

Two common polymorphisms in ERCC1, codon 118C>T and 8092C>A, have been suggested to affect ERCC1 levels.8-11 Nevertheless, no significant difference in the ERCC1 mRNA level in tumors has been described.29 Consistently, we did not find any significant relation between these SNPs and ERCC1 expression. Although no functional difference has been described for ERCC1 8092C>A polymorphism, this polymorphism has been suggested to affect ERCC1 mRNA stability, therefore, may be associated with lower DRC.30 Like XRCC1 codon 399 polymorphism, a significant gene-smoking interaction was observed for this polymorphism. Compared with the CC genotype, the AA genotype is associated with higher lung cancer risk in never smokers but lower lung cancer risk in heavy smokers. However, no significant association has been reported between the CA genotype and lung cancer risk in never smokers.23 This finding suggests that the ERCC1 8092AA but not CA genotype may not repair DNA damage efficiently, which results in higher levels of DNA damages and increased risk of lung cancer and cancer progression in never-smokers. In our study, differential RRs and PFS were observed within the ERCC1 8092C>A polymorphism. When compared gefitinib versus GP, patients with ERCC1 8092CA genotype showed higher RRs and improved PFS with gefitinib. Conversely, patients with the AA genotype showed a trend toward higher RRs to GP compared with gefitinib. If considering only patients who received GP as first-line therapy, patients with ERCC1 8092AA genotype showed a trend toward higher RR to GP compared with those with CA or CC genotypes. These findings may support the well documented disparate role of DNA repair in cancer susceptibility or progression and platinum-sensitivity.

The RRM1-37C>A and -524C>T have been reported to be associated with promoter

activity, however, no significant correlation with RRM1 expression has been reported. One retrospective analysis showed that the RR37CC-RR524TT alleotype was associated with improved survival in resected NSCLC.15 Whereas, another retrospective study in advanced NSCLC showed that the RR37AC-524CT allelotype was predictive for higher RR to gemcitabine-based chemotherapy but not survival benefit.16 In our study, none of them showed any significant association with clinical outcome even with the haplotype analysis. Instead, we found that patients with the RRM1 2464GG genotype showed higher RR and longer PFS with gefitinib compared with GP. Although no functional difference has been reported for RRM1 2464G>A polymorphism, an in vitro study has suggest that the variant allele was associated with increased sensitivity to gemcitabine.31 Considering the role of RRM1 in DNA synthesis and repair, the RRM1 2464GG genotype may have intact DRC compared with GA or AA genotypes, which may lead to higher RR and longer PFS with gefitinib.

In summary, we found that NSLA harboring SNPs related with intact DRC showed improved survival. We also indentified that these SNPs are predictive for benefit from gefitinib rather than GP. Incorporation of our findings supports a hypothesis suggesting that the intact DRC may retard molecular events related to progression in already established cancer through preventing additional multiple DNA damages, which in turn lead to benefit from gefitinib treatment and improved survival in NSLA. It may provide the first strategic clue for personalized therapy in NSLA using genotyping. Larger prospective trials that further validate and refine the predictive and prognostic utility of these SNPs are desirable.

3) Comparison of EGFR mutations between tumor cells and plasma DNA from NSCLC patients

Increasing evidence of the superiority of gefitinib in patients with sensitizing EGFR mutations has changed the paradigm of diagnosis and treatment of NSCLC patients.10-12 EGFR mutations are usually detected in tumor tissues. However, obtaining adequate tumor tissue for such analysis is often difficult, particularly in patients with refractory NSCLC. Recently, several groups have demonstrated that EGFR mutations identical to those in the corresponding tumor tissues can be detected in plasma DNA, which can be used as a biomarker for response to EGFR-TKIs.27-29 Because most patients in this study had refractory NSCLC, we did not collect tumor tissues. Instead, plasma DNA was used to identify EGFR mutation status. Although validation of the results from plasma DNA was difficult due to the limited number of paired tumor tissues, 11 cases showed concordant results among 15 paired samples. In addition, the presence of EGFR mutations was significantly predictive for higher response rates and longer survival in both arms. This finding may support the use of plasma DNA as a surrogate for tumor tissues for genetic analysis, which is clinically important.

The significance of a negative result for an EGFR mutation is highly dependent upon samples tested as well as methods performed. Direct DNA sequencing is a common detection method but has well-known sensitivity limitations depending on the proportion of tumor cells present in the material available for DNA extraction. The peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp is capable of detecting EGFR mutations in the presence of 100-fold background levels of wild-type EGFR from normal cells. Because of its high sensitivity and specificity, PNA-LNA PCR clamp is considered suitable to detect EGFR mutations in cytology samples. However, this method uses mutation-specific primers and therefore can miss rare mutations (eg, L861Q or exon 18 mutations). Additionally, the rate of detection of L858R in our study was very low compared with the rate of E746_A750del. Similar results was also reported previously using Scorpion Amplified Refractory Mutation System technology detect EGFR mutations in serum DNA. Further analyses in much larger groups of patients will be necessary to clarify the low-frequency L858R mutation could be due to assay-related false-negative findings.

4. 연구성과 및 목표달성도

(1) 연구성과

가. 국내 및 국제 전문학술지 논문 게재 및 신청

번호	논문명	저자 구분	학술 지명 (IF)	발행 년월	권,호 (쪽수)	구분	지원과제 번호
1	DNA repair gene polymorphisms and benefit from gefitinib in never-smokers with lung adenocarcinoma	제1/ 교신 저자	Cancer (5.418)	2011	in press	SCI	0810130
2	A randomized phase II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer	제1/ 교신 저자	Clin Cancer Res (6.747)	2011	in press	SCI	0810130
3	A phase II study of irinotecan, cisplatin and simvastatin for untreated extensive-disease small-cell lung cancer	제1/ 교신 저자	Cancer (5.418)	2011	in press	SCI	0810130
4	A genome-wide association study reveals susceptibility variants for non-small cell lung cancer in the Korean population.	공동 저자	Hum Mol Genet (7.386)	2010.10	Epub ahead of print	SCI	0810130
5	Simvastatin enhances irinotecan-induced apoptosis in human non-small cell lung cancer cells by inhibition of proteasome activity.	교신 저자	Invest New Drugs. (3.396)	2010 May 14	Epub ahead of print	SCI	0810130
6	Detection of low-level KRAS mutations using PNA-mediated asymmetric PCR clamping and melting curve analysis with unlabeled probes	공동 저자	J Mol Diagn (3.413)	2010.7	12 (4):418-424	SCI	없음
7	Mutational analysis of CASP10 gene in colon, breast, lung and hepatocellular carcinomas.	공동 저자	Pathology (1.142)	2010. 1	42(1):73-6	SCI	없음
8	Oncogenic NRF2 mutations in squamous cell carcinomas of oesophagus and skin.	공동 저자	J Pathol (6.466)	2010. 3	220(4):446-51	SCI	없음
9	Association of SUMO-1 and UBC9 genotypes with tumor response in non-small cell lung cancer treated with irinotecan-based chemotherapy	제1& 교신 저자	Pharmacogenomics J. (4.398)	2010. 4	10(2):86-93	SCI	0810130

10	Lovastatin overcomes gefitinib resistance in human non-small cell lung cancer cells with K-Ras mutations.	교신저자	Invest New Drugs (3.396)	2010. 12	28(6):791-9	SCI	0810130
11	A Phase II study of synchronous three-dimensional conformal boost to the gross tumor volume for patients with unresectable Stage III non-small-cell lung cancer: results of Korean Radiation Oncology Group 0301 study.	공동저자	Int J Radiat Oncol Biol Phys (4.813)	2009. 8	74(5):1397-404	SCI	없음
12	Randomized phase 2 study of subcutaneous amifostine versus epoetin-alpha given 3 times weekly during concurrent chemotherapy and hyperfractionated radiotherapy for limited-disease small cell lung cancer.	교산저자	Cancer (5.418)	2008.10	113(7):1623-31	SCI	없음
13	Association of p53 codon 72 polymorphism and MDM2 SNP309 with clinical outcome of advanced nonsmall cell lung cancer.	제1&교신저자	Cancer (5.418)	2008. 8	113(4):799-807	SCI	0810130
14	Randomized phase 2 study of irinotecan plus cisplatin versus gemcitabine plus vinorelbine as first-line chemotherapy with second-line crossover in patients with advanced nonsmall cell lung cancer.	제1저자	Cancer (5.418)	2008. 7	113(2):388-95	SCI	0810130
15	Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first : result of a randomized pilot study.	공동저자	Cancer (5.418)	2008.7	113(1):143-9	SCI	없음

16	Integrated pharmacogenetic prediction of irinotecan pharmacokinetics and toxicity in patients with advanced non-small cell lung cancer.	제1저자 & 교신저자	Lung Cancer (3.554)	2009. 1	63(1):115-20.	SCI	0810130
17	Influence of the organic anion transporting polypeptide 1B1 (OATP1B1) polymorphisms on irinotecan-pharmacokinetics and clinical outcome of patients with advanced non-small cell lung cancer	제1저자 & 교신저자	Lung Cancer (3.554)	2008. 1	59(1):69-75	SCI	0810130
18	A phase II trial of modified weekly irinotecan and cisplatin for chemotherapy-naïve patients with metastatic or recurrent squamous cell carcinoma of the esophagus	공동 저자	Cancer Chemother Pharmaco (2.654)	2008. 1	61(1):83-8	SCI	없음

나. 국내 및 국제 학술대회 논문 발표

논문명	저자	학술대회명	지역[1)]	지원과제번호
Association of p53 codon 72 polymorphism and MDM2 SNP309 with clinical outcome of advanced non-small cell lung cancer	제1저자	AACR	미국	0810130
Association of XRCC1 Arg399Gln polymorphism with tumor response and survival in never-smokers with advanced lung adenocarcinoma treated with gefitinib as the first-line therapy	제1저자	AACR	미국	0810130
Association of SUMO-1 and UBC9 genotypes with tumor response and toxicity in non-small cell lung cancer patients treated with irinotecan-based chemotherapy	제1저자	AACR	미국	0810130
irinotecan pharmacogenetics in Korean lung cancer patients	제1저자	ACOS	일본	0810130

다. 산업재산권

구분[1)]	특허명	출원인	출원국	출원번호

1) 구분 : 발명특허, 실용신안, 의장등록 등

라. 저 서

저서명	저자	발행기관(발행국, 도시)	쪽수	Chapter 제목, 쪽수 (공저일 경우)

마. 연구성과의 정부정책 기여

보고서명	정부정책	기여내용

바. 기타연구성과

(2) 목표달성도

가. 연구목표의 달성도

최종목표	연차별목표		달성내용	달성도(%)	
				연차	최종
○ 범 유전체 다형성 분석에 기초한 한국인 폐암의 약물유전체적 맞춤치료 모델 확립	1차년도	○ Whole genome-wide 분석 기반 마련 및 새로운 유전체 다형성 발굴	우리기관에서 임상시험에 참여하였던 207명의 진행성 폐암 환자의 혈액으로부터 채취한 DNA를 Affymetrix Genechip system, Mapping 500K SNP chip을 이용하여 whole genome 분석을 실시함.	90	100
		○ Cisplatin/Gemcitabine Resistance phenotype 분석	유전체 다형성 (총 7 sites) 을 분석하고 GP 항암치료 반응과의 상관관계를 관찰함. RRM1 (rs3177016, rs1042858, rs11030918, rs12806698) ERCC1 (rs3212986, rs11615) XRCC1 (rs25487) 2)ERCC1 & RRM1 immunohistochemical stain을 위한 조건 확립		
	2차년도	○ Whole genome-based SNP analysis 를 통한 한국 폐암의 새로운 SNP을 발굴 및 폐암환자 에서의 임상적 의의 분석	○ 우리기관에서 임상시험에 참여하였던 206명의 진행성 폐암 (비소세포폐암:124명, 소세포폐암:82명) 환자의 혈액으로부터 채취한 DNA를 Affymetrix® Genome-Wide Human SNP 5.0 chip을 이용하여 분석을 실시함. ○ 비소세포폐암 (124명) 환자의 생존과 치료에 대한 반응을 예측할 구 있는 유의한 SNP 분석을 실시함. 위에서 발굴한 SNP의 임상적 의의를 재 입증하기 위하여 새로운 147명의 비소세포폐암 환자의 혈액을 이용하여, 발굴된 SNP을 분석하고 임상적 관련성 분석함 ○ 소세포폐암 (79명)의 환자에서 발굴된 소세포 특이적 SNP의 임상적 관련성을 분석하였고, 이에 대한 재 입증을 위하여	90	90

			새로운 62명의 소세포폐암 환자의 혈액샘플 이용하여 2차 Affymetrix® Genome-Wide Human SNP 5.0 chip 분석을 시행함.		
		○ Cisplatin 내성형 유전자 모델 확립을 위한 임상시험의 진행 및 샘플 확보	○ DNA repair 화 관련된 ERCC1, RRM1, XRCC1 유전자의 다형성 (총 7 sites) 을 분석하고 항암치료 반응과의 상관관계를 관찰함. - RRM1 (rs3177016, rs1042858, rs11030918, rs12806698) - ERCC1 (rs3212986, rs11615) - XRCC1 (rs25487) ○ ERCC1 IHC stain 실시하고 상기 유전체 다형과의 상관관계 분석 ○ 위의 연구의 대상된 환자들의 임상적 특징이 비흡연자 폐샘암이었으므로 EGFR sensitive mutation 여부도 검사하고 상기 유전체다형성과의 관련성 분석함. ○ ERCC1 발현정도에 따른 항암치료성적 및 예후를 비교하기 위한 제 2상 임상시험이 전향적으로 진행함		
	3차년도	○ GWAS (genome-wide association study)를 통한 한국폐암 환자의 특이적 유전체 다형성 모델 확립	○ 일차 분석을 통하여 결정된 폐암 환자의 irinotecan 치료와 관련된 심각한 독성 (grade 3 diarrhea, grade 4 neutropenia)와 치료에 대한 반응 유무, 무병생존률과 전체 생존률과 유의한 관련 (P<0.00001)을 보이는 SNPs 선정함 ○ 위의 결과를 검증할 validation set 마련 및 validation 예정임	90	90
		○ 폐암 환자의 맞춤 항암치료를 위한 약물유전체 모델 확립	○ 폐암 환자에서 유전체 분석을 통한 맞춤 항암치료법 모델 제시를 위한 임상시험의 계속적 진행 ○ 임상시험에 참여하는 환자의 폐암조직과 혈장을 수집하여 항암제의 대사 및 작용표적에 관련된 대상 유전자의 발현 및 변이		

			비교 분석하고, 향후 폐암조직 대신 혈장 DNA로 대치될 가능성 평가함.		

나. 평가의 착안점에 따른 목표달성도에 대한 자체평가

평가의 착안점	자 체 평 가
○ GWAS (genome-wide association study)를 통한 한국폐암 환자의 특이적 유전체 다형성 모델 확립	○ 비소세포폐암 환자의 예후 예측인자 확립 ○ 소세포폐암 특이적 유전체 다형성 모델 확립 ○ 소세포폐암 환자의 예후 예측인자 확립
○ 폐암 환자의 맞춤 항암치료를 위한 약물유전체 모델 확립	○ 통계적으로 적절한 연구결과의 도출을 위하여 총 284명의 환자의 등록이 필요하고, 적당한 기간내 임상시험의 완료가 요구되므로 활발한 임상연구의 진행이 우선적으로 필요함. ○ 그러나 현재 경쟁적인 다른 임상연구들도 상당수 진행중이라, 대상 연구 진행의 차질을 빚을 가능성 있음. ○ 대상 유전자의 발현 및 변이 여부의 분석을 위하여 충분한 폐암조직의 수집이 필요하나, 현실적으로 폐암에서 충분한 조직 채취의 제한성 높음 (예상 조직 수집률: 약 40%, 문제점: 공격적인 조직 수집시 혈흉, 기흉 등의 부작용 우려됨)

5. 연구결과의 활용계획

(1) 연구종료 2년후 예상 연구성과

구 분	건 수	비 고
학술지 논문 게재		Clinical Cancer Research (6.747)
산업재산권 등록		특허 등록 예상 국가, 예상 특허명 등
기 타		

(2) 연구성과의 활용계획

폐암에서 항암화학요법은 가장 중요한 치료법으로 환자들의 예후 개선을 위하여 적절한 표지자의 개발을 통한 효과적인 개별맞춤요법의 접근이 절실히 필요하다. 이에 본 연구의 결과를 토대로 향후 폐암 환자들의 항암화확요법 시

1) 반응 예측
2) 독성 예측
3) 예후 예측
4) 폐암발생 위험성 예측

등의 다양한 표지자로 활용할 예정임.

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7. 첨부서류

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