기관고유연구사업 결과보고서

(과제번호 : 0510080)

폐암환자에서 약물유전체 분석을 통한 항암화학요법 감수성 예측 연구

(Pharmacogenetic prediction of chemo-sensitivity in lung cancer)

과제책임자 : 한 지 연

국 립 암 센 터

(뒷면) (측면)

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국립암센터

1. 이 보고서는 국립암센터 기관고유연구사업 결과보고서입니다.

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

제 출 문

국립암센터 원장 귀하

이 보고서를 기관고유연구사업 “ 폐암환자에서 약물유전체 분석을 통한 항암화학요법 감수성 예측 연구 (과제번호 : 0510080)” 과제의 결과보고서로 제출합니다.

2007. 12 . 20

국 립 암 센 터

과 제 책 임 자 : 한 지 연

연 구 원 : 김 진 영

목 차

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연구분야(코드)			과제번호	0510080
과 제 명	폐암환자에서 약물유전체 분석을 통한 항암화학요법 감수성 예측 연구			
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	영문	irinotecan, UGT1A, ABCB1, ABCC2, ABCG2, SLCO1B1		

◆ 연구목표

<최종목표>

- 항암제 대사에 관여하는 효소들의 유전체 다형성 분석을 통한 항암치료 반응 및 독성 예측 방법 개발
- 한국 폐암 환자의 유전체다형성 분석을 통한 예후인자 개발
- 한국 폐암 환자의 특이적 유전체 다형성에 따른 최적의 맞춤항암요법 모델 개발 및 임상적 적용이 가능한 kit 개발

<당해년도 목표>

1) 항암제 대사에 관여하는 효소들의 유전체 다형성 분석을 통한 항암치료 반응 및 독성 예측 방법 개발

2) 한국 폐암 환자의 유전체다형성 분석을 통한 예후인자 개발

◆ 연구내용 및 방법

1. 진행성 폐암 환자의 생존률을 증가시키기 위한 새로운 임상시험을 개발하여 임상시험에 자발적으로 참여하고, 약물유전체 연구를 위하여 혈액샘플을 공여하는데 동의한 환자들로부터 혈액샘플을 공여 받아 수집함.

2. 항암제 대사 및 이동에 관여하는 주요 효소 및 transporter 들의 유전체 다형성을 direct sequencing을 이용하여 분석함.

   A) metabolizing enzyme: UGT1A1, UGT1A6, UGT1A7, UGT1A9, CYP3A5

      irinotecan 의 metabolizm에 관여하는 UGT1A의 다양한 subtype 및 CYP3A5의 유전체 다형성 분석

B) Drug transporter genes

1) Bile canalicular membrane 에 발현함으로써 irinotecan 및 대사체의 biliary excretion에 관여하는 ABC transporters 유전체 다형성 분석

ABCB1: 1236C>T, 2677G>T/A, 3435C>T

ABCC2: -24C>T, 1249G>A, 3972C>T

ABCG2: 34G>A, 421C>A

2) SLCO1B1: basolateral membrane of hepatocyte에 발현하여 약물의 대사 및 배설 전에 hepatocye uptake & accumulation 에 관여하는 SLCO1B1 -11187G>A, 388A>G, 521T>C 다형성 분석

C) 폐암환자 예후 예측을 위한 유전체 다형성 분석

1) p53 codon 72 polymorphism

2) MDM2 SNP309

3) IGFBP3 gene polymorphism vs. plasma levels of IGF-1, IGF-2, & IGFBP3

4) SUMO & UBC9 polymorphisms

◆ 연구성과

-정량적 성과

구분	달성치/목표치	달성도(%)
SCI 논문 편수	16/9	178%
IF 합	91.493/32.8	279%

-정성적 성과

irinotecan은 폐암에 효과적인 항암제로 널리 사용되고 있으나, 간혹 백혈구감소증, 설사와 같은 치명적인 독성이 발생할 수 있다. 이에 본 3년간의 연구를 통하여 irinotecan 대사 및 이동에 관여하는 각종 유전체의 다형성을 분석함으로써 환자 개인별 irinotecan 약동학의 차이와 이에 따른 심한 독성을 예측할 수 있는 통합적인 약물유전체 모델을 확립하였다.

◆ 참여연구원 (최종연도 참여인원)	성 명	김진영, 이주연
	주민등록번호	

Project Summary

Title of Project	Pharmacogenetic prediction of chemo-sensitivity in lung cancer
Key Words	Irinotecan, UGT1A, ABCB1, ABCC2, ABCG2, SLCO1B1
Project Leader	Ji-Youn Han
Associated Company	

Background: We evaluated multivariate analysis using 15 polymorphisms within seven genes with putative influence on metabolism and transport of irinotecan to define an integrated pharmacogenetic model for predicting irinotecan pharmacokinetic (PK) and severe toxicity.

Methods: A total of 107 Korean NSCLC patients treated with irinotecan and cisplatin chemotherapy were evaluated for irinotecan-PK and genotyped for the UGT1A1 *6, UGT1A1*28, UGT1A9*22, ABCB1 1236C>T, 2677G>T/A, 3435C>T, ABCC2 -24C>T, 1249G>A, 3972C>T, ABCG2 34G>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 wereperformed to identify final independent predictive factors for irinotecan-PK and severe toxicities.

Results: Among several irinotecan-PK parameters, only SN-38 AUC was significantly correlated with nadir neutrophil counts (r=-0.3, p=0.009) and grade 4 neutropenia (p=0.01). Multivariate analysis identified that UGT1A1*6/*6, UGT1A9*1/*1 or *1/*22, and SLCO1B1 521TC or CC genotypes, and female gender were predictive for higher AUCSN-38. Among them, SLCO1B1 521TC 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 irinotecan-PK parameters and grade 3 diarrhea, the UGT1A9*1/*1, ABCC2 3972CC, and ABCG2 34GA or AA genotypes were independentlypredictive for grade 3 diarrhea in multivariate analysis (OR=6.3, 5.6, and 5.1, respectively).

Conclusions: Patient selection based on integrated pharmacogenetic model would be helpful for predicting irinotecan-PK and severe toxicities in NSCLC patients treated with irinotecan-based chemotherapy.

1. 연구사업의 최종목표

- 항암제 대사에 관여하는 효소들의 유전체 다형성 분석을 통한 항암치료 반응 및 독성 예측 방법 개발
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- 임상적 적용이 가능한 kit 개발

2. 연구사업의 내용 및 결과

<METHODS>

- **Patients**

From September 2002 to June 2005, a total of 107 chemo-naïve patients with advanced NSCLC who were prospectively enrolled into two different clinical trials of irinotecan plus cisplatin (IP) chemotherapy, participated in irinotecan-pharmacokinetic (PK) study.14, 15 Patients were required to have: (1) pathologically confirmed stage IIIB with pleural effusion or stage IV NSCLC (2) Eastern Cooperative Oncology Group performance status 0 to 2; (3) adequate organ function: (i) hematology: absolute neutrophil count ■2.0 x 109/L, platelets ■ 150 x 109/L, (ii) hepatic: serum bilirubin (bili) 1.0x the upper limit of normal (ULN), AST/ALT 1.5x ULN, alkaline phosphatase or gamma-glutamyltransferase 2.5x ULN, (iii) renal: serum creatinine 1.5 mg/dl; (4) no prior chemotherapy. The characteristics of the 107 patients are presented in Table 1. All patients signed written informed consent approved by the Institutional Review Board of the National Cancer Center Hospital. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

- **Treatment**

Patients received irinotecan on days 1 and 8 every 3-weeks as a 90-minute intravenously infusion at doses of 80 mg/m2 (n=81) or 65 mg/m2(n=26). Patients received prophylactic antiemetics. For the treatment of irinotecan-induced delayed diarrhea, patients received loperamide, and antibiotics, if necessary.

- **Pharmacokinetic study**

For pharmacokinetic analysis, 10 ml of venous blood was taken into sodium heparinized evacuated tubes on day 1 of cycle 1 before irinotecan infusion, and at 30, 60, 65, 75, 90,

105 min and 2, 3, 5, 7, 25 h after the start of irinotecan infusion. Total plasma concentrations (i.e., the total of lactone and carboxylate) of irinotecan and its metabolites SN-38, SN-38G, and APC were determined by reversed-phase high-performance liquid chromatography with fluorescence detection, using a modification of a procedure described previously.14 Individual plasma concentrations of irinotecan and metabolites were analyzed using noncompartmental methods as implemented in the computer software program WinNonlin version 4.0 (Pharsight, Inc., Mountain View, CA).

- **Analysis of polymorphisms**

Blood samples for genotyping were taken before chemotherapy. Genomic DNA was extracted from whole blood using DNA Purification kit (Gentra, MN, USA). The UGT1A1 211G>A (*6), UGT1A1*28, UGT1A9 -118(T)9>10 (*22), ABCC2 24C>T, 1249 G>A, and 3972 C>T, and SLCO1B1 11187G>A, 388A>G, and 521T>C, and CYP3A5 22893G>A (*3) polymorphisms were investigated using the single base primer extension assay using ABI Prism SNaPShot Multiplex kit (ABI, Foster City, CA, USA). The ABCB1 1236C>T and 3435C>T, and ABCG2 421C>A, were genotyped by the TaqMan assay (Applied Biosystems., CA, USA) and the ABCB1 2677G>T/A and ABCG2 34G>A polymorphisms were screened by direct sequencing (ABI 3730 DNA sequencer, Perkin-Elmer, CA, USA). The assay, primer sequences, and restriction enzyme for studying polymorphisms performed were described previously.11-13

- **Statistical Analysis**

Mann-Whitney U test was used to compare continuous variables. Spearman's rank correlation was used for relating two continuous variables. The 2 test or Fisher's exact test was used to compare proportions of patients for clinicopathologic and genotype factors. Variables with the P values less than 0.1 on univariate analysis were considered for possible inclusion in a multivariable analysis. Statistical analyses were performed using SPSS and two-sided p-values <0.05 were considered significant.

<RESULTS>

A total of 107 patients were assessable for PK and pharmacogenetic analysis. Patients' characteristics and overallfrequencies of the examined polymorphisms are presented in Table 1. No significant association between polymorphisms and clinicopathologic factors such as gender, stage, tumor histology, and smoking status was observed (data not shown).

- **Irinotecan pharmacokinetics and toxicity**

We evaluated the association of irinotecan-induced severe toxicities and irinotecan-PK parameters for all 107 patients. The most common severe toxicity was NCI-CTC grade 4 (G4) neutropenia, which occurred in 26 (24%) patients. The neutropenia was defined as the lowest point during follow-up (nadir), and the nadir absolute neutrophil counts (ANC) were correlated negatively with AUCSN-38 (r=-0.3, p=0.009, data not shown). Patients with G4 neutropenia were associated with significantly higher AUCSN-38 (p=0.013, Table 2), whereas, there was no significant relationship between grade 3 diarrhea and any PK-parameters (data not shown except AUC, Table 2).

- **Genotype and SN-38 AUC**

Because only SN-38 AUC was significantly associated with grade 4 neutropenia, we analyzed the association of SN-38 AUC with genotypes as well as patients' clinicopathologic factors. By genotype, the UGT1A1*6/*6 (p=0.0001), UGT1A9*1/*1 or *1/*22 (p=0.003), and SLCO1B1521TC or CC (p=0.005) genotypes were significantly associated with higher AUCSN-38. The ABCB1 2677GG, GT, or GA (p=0.072), and SLCO1B1 11187GA or AA genotypes (p=0.084) also showed a trend towards higher AUCSN-38. In a multivariate analysis including covariates listed in Table 2 with P<0.1 as possible predictors of AUCSN-38, the UGT1A1*6/*6 (p<0.0001), UGT1A9*1/*1 or *1/*22 (p=0.011), and SLCO1B1 521TC or CC (p=0.017) variants, and female gender (p=0.036) were independently predictive for higher AUCSN-38 (Table 4).

- **Genotype and toxicity**

We examined the association of patients' clinicopathologic factors as well as genotypes with severe toxicities for all 107 patients enrolled (Table 5). Patients with UGT1A1*6/*6 (p=0.009), ABCB1 2677GG, GT, or GA (p=0.025), SLCO1B1-11187 GA or AA (p=0.038), and SLCO1B1 521TC or CC genotypes (p=0.004) those were associated with higher SN-38 AUC, were significantly prevalent in G4 neutropenia. Patients with UGT1A9*1/*1 or *1/*22 (p=0.052) and SLCO1B1 388GG genotypes (p=0.072) also showed a trend towards higher incidence of G4 neutropenia. In a multivariate analysis including all covariates listed in Table 4 with P<0.1, the SLCO1B1 521TC or CC (Odds ratio (OR)=3.8, p=0.007) and UGT1A1*6/*6 genotypes (OR=7.4, p=0.028) were independently predictive for G4 neutropenia (Table 6).

Grade 3 (G3) diarrhea was developed in 11 (10%) patients. No apparent relationship was observed between AUC of irinotecan and its metabolites and G3 diarrhea (Table 2). Univariate analysis identified the UGT1A9*1/*1 (p=0.048), ABCC2 3972CC genotypes (p=0.024) were significantly associated with G3 diarrhea (Table 5). The ABCG2 34GA or

AA genotypes also showed a trend toward higher incidence of G3 diarrhea (p=0.054). Multivariate analysis including these covariates with P<0.1, demonstrated that UGT1A9*1/*1 (OR=6.3), ABCC2 3972CC (OR=5.6), and ABCG2 34GA or AA genotypes (OR=5.1) were independent predictive for G3 diarrhea (Table 6).

3. 연구결과 고찰 및 결론

Irinotecan is characterized by a wide interpatient variability in pharmacokinetics (PK) and subsequent pharmacologic effects and toxicity.1 It is metabolized by carboxylesterase to form an active metabolite, SN-38, which is further conjugated and detoxified by uridine diphosphate glucuronosyltransferase 1A (UGT1A) to yield SN-38 glucuronide (SN-38G).2, 3 Irinotecanis also subject to oxidation by the cytochrome P450 3A (CYP3A) family, which catalyzes the formation of inactive metabolites such as APC and NPC.4, 5NPC may be further metabolized into SN-38 by carboxylesterase.6 Beside the hepatic metabolizing enzymes, drug transporters have been implicated in the disposition of irinotecan and its metabolites, as well. The ATP-binding cassette (ABC) transporters such as, ABCC2 (cMOAT, MRP2) and a lesser extent, ABCB1 (MDR1) and ABCG2 (BCRP), present on the bile canalicular membrane, are responsible for facilitating biliary excretion of irinotecan and its metabolites.7-9 In addition, the organic anion transporting polypeptides (OATPs) are expressed on the basolateral domain of hepatocytesand facilitate the uptake of drugs before their eliminationinto bile. Among several isoforms, the OATP1B1 is supposed to be involved in the hepatic transport of SN-38.10 Previously we conducted exploratory irinotecan pharmacogenetic analysesusing several polymorphisms in UGT1A1, UGT1A9, ABCB1, ABCC2, ABCG2, and SLCO1B1 genes, and evaluated their significance in NSCLC patients separately.11-13 However, irinotecan pharmacology is complex and may be dependent on the interplay of metabolizing enzymes and transporters. Moreover, altered function caused by singlegene variation can be obscured by the compensatory activity of other enzymes and transporters. Therefore, metabolizing enzymes, transporters, and other potential regulatory factors should be viewed and evaluated as an integratedsystem rather than single component for the accurate prediction of irinotecan-PK and toxicity. To define an integrated pharmacogenetic model for predicting irinotecan PK and severe toxicities in NSCLC patients treated with irinotecan plus cisplatin chemotherapy, we conducted this multivariate analysis using 15 polymorphisms within seven genes with putative influence on metabolism and transport of irinotecan and its metabolites as well as patients' clinicopathologic factors.

In the present study, we have attempted a more comprehensive pathway evaluation to

identify genetic variants and patterns that may help predict irinotecan-related severe toxicities, thus ultimately leading to a more tailored approach to irinotecan-based chemotherapy. Moreover, we included other potential clinicopathologic factors in this model to provide further extended data that might help understanding inter-patient variability of irinotecan-PK and subsequent occurrence of severe toxicity.

The relationship between PK parameters and irinotecan-related severe neutropenia and diarrhea has been studied extensively, however, the findings are highly variable, and the final conclusion cannot be drawn yet.16 In the current study, the nadir ANC is negatively correlated with AUCSN-38 (r=-0.3, p=0.009) and patients experienced grade 4 neutropenia were related with significantly higher SN-38 AUC (p=0.01, Table 2). In a multivariate analysis, we found that the UGT1A1*6/*6 and SLCO1B1 521TC or CC genotypes those were significantly associated with higher SN-38 AUC, were independently predictive for grade 4 neutropenia. These findings are in concordance with our previous reports from irinotecan pharmacogenetic studies.11, 13 Regarding UGT1A1*28, the frequency is relatively low in Asians. Indeed, there was no homozygous UGT1A1*28, thus, we could not completely rule out the functional importance of UGT1A1*28 in the current study.

The occurrence of severe diarrheahas significantly complicating results and can be life threatening.1, 17 Although the pathogenesis of irinotecan-induced delayed diarrhea is controversial, it has been supposed that diarrhea is a function of the intraluminal exposure to SN-38 due to excessive biliary excretion of SN-38.18 Some reports suggest thatbiliary index (BI) of SN-38, which is a surrogate measure of SN-38 biliary excretion was calculated as (AUC SN-38/AUC SN-38G) x AUC CPT-11, to be directly related to irinotecan-induced severe diarrhea,18, 19but this could not confirmed in other studies.20-22 While no significantchange in BI in relation with severe diarrhea was observed in the current study (data not shown), patients with UGT1A9*1/*1 was significantly associated with higher BI than those carrying UGT1A9*22 allele (median BI, 786.2 versus 405.7 ng*h/ml/mg, p=0.005, data not shown), which may contribute to develop severe diarrhea in patients carrying UGT1A9*1/*1. In addition, UGT1A9 is expressed in a number of extrahepatic tissues including lower gastrointestinal tract such as jejunum, ileum, colon, and rectum as well as in the liver.23 Because SN-38 glucuronidation in the gastrointestinal tract is also important for the development of severe diarrhea, the UGT1A9*1/*1 genotype, which is significantly associated with decreased glucuronidation activity, can cause increased intraluminal exposure of SN-38, and subsequent development of severe diarrhea.24, 25

ABCC2 is expressed in the apical membrane of hepatocyte and appears to be the principal transporter involved in hepatobiliary excretion of irinotecan and its metabolites. Alteration of this transporter system causes Dubin-Johnson syndrome characterized by

conjugated hyperbilirubinemia and multiple functional polymorphisms have been described.26 We found that ABCC2 3972C>T variant was associated with grade 3 diarrhea. The homozygous for wild type (CC) was significantly predictive for grade 3 diarrhea than CT or TT genotypes (OR=5.6, p=0.041). Innocenti et al. reported that ABCC23972TT genotype was associated with higher AUC of irinotecan (p=0.02), APC and SN-38G (both p<0.0001) compared with CC or CT genotypes, suggesting that ABCC23972C>T variant is associated with reduced hepatobiliary excretion of irinotecan and its metabolites.27 While no significant change in irinotecan-PK was observed in relation with ABCC2 polymorphisms in the current study, the relatively higher biliary excretion activity in patients with homozygous wild type may be associated with higher frequency of grade 3 diarrhea.

We also found that ABCG2 34G>A variant is associated with grade 3 diarrhea. ABCG2 is endogenously expressed at high levels in human placenta, the small intestine and colon, and the bile canalicular membrane.26 This localization suggests that the physiologic role of ABCG2 may be to regulate intestinal absorption and biliary secretion of irinotecan and its metabolites by active transport mechanisms.28 Recently, Cusatis et al. investigated the association between ABCG2 variants and diarrhea in gefitinib-treated patients. Patients with at least one copy of ABCG2 421C>A had a much higher rate of diarrhea than those lacking it.29 In the current study, no significant association between ABCG2421C>A and diarrhea was observed. Instead, patients carrying at least one ABCG2 34A allele developed more grade 3 diarrhea than homozygous for wild type. In a multivariate analysis, this variant was independently predictive for grade 3 diarrhea (OR=5.1, p=0.038). Evidence for reduced drug efflux activity of ABCG2 34G>A variant comes from an in vitro study using polarized LLC-PKI cells. This polymorphism impaired the specific apical membrane localization of this transporter, leading to decreased drug efflux activity.30 This finding suggests that ABCG2 34G>A variants may be less efficient at pushing irinotecan and/or its metabolites out of cells in the intestine and associated with the higher occurrence of diarrhea.

In summary, integrated pathway analysis including metabolizing enzymes and transporters may provide a more reliable pharmacogenetic model for predicting PK and severe toxicities in patients treated with irinotecan. However, caner is a complex disorder caused by multiple genetic factors, therefore, the understating of the precise role of all participating factors is still limited. 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.

4. 연구성과 및 목표달성도

(1) 연구성과

가. 국내 및 국제 전문학술지 논문 게재 및 신청

논문명	저자 (저자구분)	저널명(I.F.)	Vol(No)Page	구분	과제 관련 성
Thymidine phosphorylase expression in tumour cells and tumour response to capecitabine plus docetaxel chemotherapy in non-small cell lung cancer.	제1저자	J Clin Pathol (2.619)	58(6):650-4	국외 SCI	중
Hypoxia-inducible factor 1 alpha and antiangiogenic activity of farnesyltransferase inhibitor SCH66336 in human aerodigestive tract cancer.	제1저자	J Natl Cancer Inst (13.856)	97(17):1272-86	국외 SCI	하
9-cis-retinoic acid treatment increases serum concentrations of alpha-tocopherol in former smokers.	제1저자	Clin Cancer Res (5.623)	11(6):2305-1	국외 SCI	하
Effects of 9-cis-retinoic acid on the insulin-like growth factor axis in former smoker	공동저자	J Clin Oncol (9.835)	23(19):4439-4	국외 SCI	하
Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in non-small cell lung cancer patients treated with irinotecan and cisplatin	제1저자	J Clin Oncol (13.598)	24(15):2237-2244	국외 SCI	상
Randomized Phase II Study of Two Opposite Administration Sequences of Irinotecan and Cisplatin in Patients with Advanced Non-small Cell Lung Carcinoma	제1저자	Cancer (4.582)	106(4):873-880	국외 SCI	상
The prognostic significance of pretreatment plasma levels of insulin-like growth factor (IGF)-1, IGF-2, and IGF binding protein-3 in patients with advanced non-small cell lung cancer.	제1저자 교신저자	Lung Cancer (3.554)	54(2):227-234	국외 SCI	상
Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer	제1저자 교신저자	Cancer (4.582)	110(1):138-47	국외 SCI	상

논문명	저자 (저자구분)	저널명(I.F.)	Vol(No)Page	구분	과제 관련 성
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)	2007 (in press)	국외 SCI	상
Integrated pharmacogenetic prediction of irinotecan pharmacokinetics and toxicity in patients with advanced non-small cell lung cancer	제1저자 교신저자	Lung Cancer (3.554)	게재 신청	국외 SCI	상

나. 국내 및 국제 학술대회 논문 발표

논문명	저자	학술대회명	지역	과제 관련성
Randomized phase II study comparing the sequence of irinotecan and cisplatin administration in chemo-naïve patients with advanced non-small cell lung cancer	제1저자	ASCO	미국	상
Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in non-small cell lung cancer patients treated with irinotecan and cisplatin	제1저자	약물유전체 연구집담회	서울	상
Thymidine Phosphorylase Expression in Tumor Cells and Tumor Response to Capecitabine plus Docetaxel Chemotherapy in Non-Small Cell Lung Cancer	제1저자	AACR	미국	중
Phase II study of irinotecan/cisplatin induction followed by concurrent twice-daily thoracic irradiation with etoposide/cisplatin chemotherapy for limited disease small cell lung cancer	제1저자	대한암학회	서울	중
The prognostic significance of pretreatment plasma levels of insulin-like growth factor (IGF)-1, IGF-2, and IGF binding protein-3 in patients with advanced non-small cell lung cancer.	제1저자	AACR	미국	상
Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in non-small cell lung cancer patients treated with irinotecan and cisplatin	제1저자	ASCO	미국	상
Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer	제1저자	AACR	미국	상

논문명	저자	학술대회명	지역	과제 관련성
Pharmacogenetic prediction for tumor response, toxicity, and survival of NSCLC patients treated with irinotecan and cisplatin chemotherapy	제1저자	ASCO	미국	상
Pharmacogenetic prediction of irinotecan pharmacokinetics and pharmacodynamics in patients with advanced non-small cell lung cancer	제1저자	World Conference of Lung Cancer	한국	상
Integrated pharmacogenetic prediction of irinotecan pharmacokinetics and pharmacodynamics in patients with advanced non-small cell lung cancer	제1저자	Asian Lung Cancer Forum	싱가폴	상

다. 산업재산권

구분	특허명	출원인	출원국	출원번호
없음.				

※구분 : 발명특허, 실용신안, 의장등록 등

라. 저 서

저서명	저자	발행기관(발행국, 도시)	쪽수	Chapter 제목, 쪽수 (공저일 경우)
Lung Cancer, 3rd edition	한지연, 이대호, 이진수	미국, MA	2008 in press	bronchioloalveolar carcinoma

마. 연구성과의 정부정책 기여

보고서명	정부정책	기여내용
없음.		

바. 기타연구성과

없음.

(2) 목표달성도

가. 연구목표의 달성도

최종목표	연차별목표		달성내용	달성도(%)	
				연차	최종
- 약물유전체 연구를 통한 항암치료 반응 및 독성 예측방법 개발 - 한국 폐암 환자의 유전체다형성 분석을 통한 예후인자 개발 - 한국 폐암 환자의 특이적 유전체 다형성에 따른 최적의 맞춤항암요법 모델 개발 및 임상적 적용이 가능한 kit 개발	1차 년도	- 폐암환자에서 Irinotecan 대사에 관여하는 각종 효소 유전체 다형성 분석 - Irinotecan 항암치료의 독성, 반응 및 예후 예측인자 개발	- Irinotecan 대사에 관여하는 주요 효소 유전체 다형성 분석함. - irinotecan-based chemotherapy 시 심한 독성, 항암치료반응 및 예후를 예측할 수 있는 UGT1A 유전체 다형성 모델을 확립함.	95	30
	2차 년도	- Irinotecan transport에 관여하는 유전체 다형성 분석을 통한 항암치료 반응 및 독성 예측 방법 개발 - 한국 폐암 환자의 예후인자 개발	- irinotecan-based chemotherapy 시 심한 독성, 항암치료반응 및 예후를 예측할 수 있는 ABCB1, ABCC2, SLCO1B1 유전체 다형성 모델을 확립함. - 진행성 폐암환자의 예후예측인자로 IGF-1, IGF-2 IGFBP-3 혈장 범위를 결정함.	95	65
	3차 년도	- Irinotecan 대사 및 이동에 관여하는 유전체 다형성 분석 및 다변수 분석을 통한 항암치료 반응 및 독성 예측 방법 개발 - p53 pathway 관련 유전체 다형성 분석을 통한 폐암환자의 치료반응 및 예후 예측인자 개발	- irinotecan 대사 및 이동에 관여하는 각종 유전체의 다형성을 분석함으로써 환자 개인별 irinotecan 약동학의 차이와 이에 따른 심한 독성을 예측할 수 있는 통합적인 약물유전체 모델을 확립함. - p53 codon 72 polymorphism & MDM2 SNP309 분석 및 예후인자로서의 가능성 분석	95	95

나. 평가의 착안점에 따른 목표달성도에 대한 자체평가

평가의 착안점	자 체 평 가
오랜 시간과 많은 노력을 요하는 임상시험의 기초 하에 진행 된 highly qualified 연구임.	3년간에 걸친 다양한 임상시험의 진행과 이를 통한 약물유전체 연구를 통하여 캠푸토 사용 시 부작용을 최소화 할 수 있는 약물유전체 모델을 확립함.
전향적 임상연구를 통한 연구로 자료의 객관성이 확립됨.	객관적 자료를 이요한 통계적 검증으로 최종 모델 확립함. 앞으로 확립된 약물유전체모델의 타당성 점검을 위한 모두 많은 수의 환자를 통한 임상연구가 필요함. 임상적으로 용이하게 사용할 수 있는 방법을 마련하도록 함이 필요함.

5. 연구결과의 활용계획

(1) 연구종료 2년후 예상 연구성과

구 분	건 수	비 고
학술지 논문 게재	3	Cancer (4.582) X 3 = 13.746
산업재산권 등록	없음.	
기 타	없음.	

(2) 연구성과의 활용계획

- 최종적으로 107명의 임상연구를 자료를 이용하여 integrated pharamcogenetic model을 확립하였으나, 본 모델의 타당성 검증을 위하여 보다 많은 수의 환자가 참여하는 임상연구의 진행 및 이를 통한 타당성 입증이 필요함.

- 현재까지 캠푸토 한 가지 약물에 대한 연구가 이뤄졌으나, 폐암에서 사용하는 다양한 항암제들의 반응과 독성을 예측할 수 모델의 확립이 필요함. 이에 보다 다양한 유전체의 분석을 위하여 Whole genome-wide analysis 가 필요함.

- 항암제의 반응과 독성을 예측할 수 있는 향상된 유전체 모델 확립을 위하여 tumor 와 host 의 genetic variation을 모두 분석하는 것이 필요함.

- Pharamcogenetic strategy의 효능 평가를 위한 임상시험의 진행이 필요함.

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7. 첨부서류

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1	Thymidine phosphorylase expression in tumour cells and tumour response to capecitabine plus docetaxel chemotherapy in non-small cell lung cancer.
2	Hypoxia-inducible factor 1 alpha and antiangiogenic activity of farnesyltransferase inhibitor SCH66336 in human aerodigestive tract cancer.
3	9-cis-retinoic acid treatment increases serum concentrations of alpha-tocopherol in former smokers.
4	Effects of 9-cis-retinoic acid on the insulin-like growth factor axis in former smoker
5	Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in non-small cell lung cancer patients treated with irinotecan and cisplatin
6	Randomized Phase II Study of Two Opposite Administration Sequences of Irinotecan and Cisplatin in Patients with Advanced Non-small Cell Lung Carcinoma
7	The prognostic significance of pretreatment plasma levels of insulin-like growth factor (IGF)-1, IGF-2, and IGF binding protein-3 in patients with advanced non-small cell lung cancer.
8	Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer
9	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