Comparison of docetaxel/cisplatin dosages of 75/60 and 60/60 mg/m^2 for the treatment of non-small cell lung cancer

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Received March 28, 2012; Accepted May 28, 2012

DOI: 10.3892/etm.2012.597

Abstract. A combination of docetaxel (D) and cisplatin (P) is one of the standard regimens for the initial treatment of advanced non-small cell lung cancer (NSCLC). Yet, the toxicity of D administered at 75 mg/m^2 in three weekly doses to patients is a concern. The aim of this study was to assess the efficacy of a lower combination dose, 60 mg/m^2 of D and 60 mg/m^2 of cisplatin (P), as a treatment for NSCLC. In this randomized, phase III trial, we compared the response rates (RRs) and toxicity profiles of two combination regimens, D/P 75/60 vs. 60/60 mg/m^2, to patients with stage IIIB or IV NSCLC. A total of 132 patients were randomized to the 75/60 (n=65) or 60/60 (n=67) dosage group. Non-inferiority of 60/60 group compared to the 75/60 group was confirmed by the RR (38.5% for the 75/60 group and 40.3% for the 60/60 group, 95% confidence interval -14.8 to 18.5, meeting the predefined non-inferiority criterion). The dose reduction rate and incidence of grade 3-4 neutropenia were significantly higher in the 75/60 group. The incidence of neutropenia was significantly higher in those with the non-expressing genotype (GG) compared to the AG or AA genotypes of CYP3A5. We determined that DP 60/60 was not inferior to DP 75/60 in RR, and that the reduced combination dosage provides a better safety profile for patients.

Introduction

A combination of docetaxel (D) and cisplatin (P) is one of the standard regimens for the initial treatment of advanced non-small cell lung cancer (NSCLC). The landmark Eastern Cooperative Oncology Group (ECOG) 1594 (1) and Tax 326 (2) studies used three weekly D doses of 75 mg/m^2. Whereas in a Japanese phase II trial (3), three weekly doses of 60 mg/m^2 were used. In Korea, the recommended dose of D for NSCLC is 75 mg/m^2 in three weekly doses. Because of toxicities associated with 75 mg/m^2 of D, there have been concerns related to using this dosage in the Korean population.

The primary objective of this study was to evaluate the efficacy of a lower D dose of 60 mg/m^2 with 60 mg/m^2 P as a first-line treatment for NSCLC compared to the 75 mg/m^2 D dose with 60 mg/m^2 P. We also performed single-nucleotide polymorphism (SNP) analysis of the cytochrome (CYP)3A5, CYP3A4 and the ABCB1 genes in the patients to evaluate any toxicity profile differences or responses according to genotypes.

D is eliminated mainly by hepatic CYP450, CYP3A4 and CYP3A5 (4). The presence of a SNP in the 5'-regulatory region of the CYP3A4 gene (-392A>G), referred to as CYP3A4*1B, has been associated *in vitro* with enhanced CYP3A4 expression (5), and a CYP3A5*3 polymorphism (A6986G) has been shown to lead to an inactive truncated protein (6).

Moreover, intestinal P-glycoprotein (P-gp, multidrug resistance 1, ABCB1) plays a main role in fecal elimination of D by modulating reabsorption of the drug after hepatobiliary secretion (7). Reduced clearance of D has been associated with an increased risk of hematologic toxicity (8). The silent ABCB1 3435C>T polymorphism has been associated with a lower expression of P-gp (9). Another polymorphism of the ABCB1 gene, G2677T/A, has also been reported as a predictor of response to D chemotherapy (10). Although controversy exists, 2677GG and 3435CC genotypes have been associated with a better chemotherapy response and increased D-related toxicity, probably due to lower P-gp expression levels (10).

Patients and methods

Study design. In this phase III trial, chemotherapy-naive patients with stage IIIB or IV NSCLC were randomized into one of two arms, respectively. The control arm received 75 mg/m^2 of D and 60 mg/m^2 of P in three weekly doses (75/60 group). The experimental arm followed the same schedule and received

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Key words: non-small cell lung carcinoma, docetaxel, cisplatin, cytochrome P-450, CYP3A5

Table I. Primers and enzymes for CYP3A and ABCB1 polymorphism analysis.

SNP	Primers (5'→3')	Enzyme	Size (bp)
CYP3A4 (-392A>G)	F, TGAGGACAGCCATAGAGACAAGG R, CAAGGGTTCTGGGTTCTTATCA	Direct sequencing	98
CYP3A5 (A6986G)	F, ACCACCCAGCTTAACGAATG R, ATGTGGTCCAAACAGGGAAG	Direct sequencing	98
ABCB1 exon 21 G2677A	F, TGCAGGCTATAGTTCCAGG R, GTTTGACTCACCTTCCCAG	*Rsa*I	220
ABCB1 exon 21 G2677T	F, TGCAGGCTATAGTTCCAGG R, TTTAGTTTGACTCACCTTCCCG	*Ban*I	224
ABCB1 exon 26 C3435T	F, TGTTTTCAGCTGCTTGATGG R, AAGGCATGTATGTTGGCCTC	*Sau*3AI	197

F, forward; R, reverse. bp, base pair.

the same amount of P but only 60 mg/m^2 of D (60/60 group). The randomization was stratified in accordance with ECOG performance scale (PS) 0-1 vs. 2, weight loss in the previous 6 months <5 vs. ≥5%, and stage IIIB vs. IV or relapsed.

The primary endpoint of the study was to evaluate the non-inferiority of the experimental arm in terms of the response rate as measured by the Response Evaluation Criteria in Solid Tumors (RECIST). The non-inferiority margin was set at -15%. Ninety-five percent confidence interval for the difference between two proportions was calculated according to the method described by Newcombe (11) without a correction for continuity. Secondary endpoints were progression-free survival and safety.

A neutrophil count ≥1,500/μl and a platelet count ≥100,000/μl were required to receive the next dose. A 20% dosage reduction was allowed for grade 4 hematologic toxicities or for grade 3 or 4 non-hematologic toxicities. Treatment could be delayed up to two weeks. Toxicity was evaluated with the National Cancer Institute Common Toxicity Criteria version 3.0.

This study was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (#HCRE 07-018-3) (Jeonnam, Korea) and written informed consent was obtained from all patients.

Patient selection. Enrolled patients met the following inclusion criteria: stage IIIB/IV or relapsed NSCLC, ≥18 years of age, ECOG performance status 0-2, presence of uni-dimensionally measurable lesion(s) by RECIST version 1.0 (12), no prior chemotherapy or radiotherapy for NSCLC, no other previous investigational therapy, adequate bone marrow function, adequate liver and renal function, no prior malignancy and written informed consent.

Exclusion criteria included: carcinoid tumors, small-cell carcinoma of the lung, a history of another malignancy within the last five years (except cured basal cell carcinoma of the skin and cured carcinoma *in situ* of the uterine cervix), any other morbidity or situation with contraindications for chemotherapy (e.g. active infection, myocardial infarction in the preceding six months, symptomatic heart disease including unstable angina, congestive heart failure or uncontrolled arrhythmias, immunosuppressive treatment), pregnant or lactating women, and women and men of childbearing potential who did not wish to use adequate contraception.

Definitions of the study populations were as follows. The intent to treat (ITT) population included 132 patients who were randomized and treated with at least one cycle of chemotherapy. All randomized patients received at least one cycle of chemotherapy. A safety evaluation was performed in this population. The response evaluable (RE) population included 119 patients whose responses were evaluated.

Polymorphism analysis. Genomic DNA samples were obtained from 87 patients. DNA was isolated from 0.5 ml EDTA-treated whole blood using a QIAamp DNA Blood Midi kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. Primers and enzymes used for the CYP3A and ABCB1 polymorphism analyses are listed in Table I. The observed frequency of each genotype was compared with the expected frequency using a χ^2 test (Hardy-Weinberg equilibrium).

Genotyping of CYP3A4 (-392A>G, RefSNP, rs2740574) and CYP3A5 (A6986G, RefSNP, rs776746). Genotyping of *CYP3A4* and *CYP3A5* was determined by polymerase chain reaction (PCR) followed by direct sequencing. PCR was performed using a Takara PCR Thermal Cycler Dice TP600 (Takara Shuzo, Tokyo, Japan). Amplified DNA was purified using a QIAquick DNA purification system (Qiagen). Genotyping for the CYP3A4*1A/*1A, CYP3A4*1A/*1B and CYP3A4*1B/*1B genotypes (AA, AG and GG, respectively, at nucleotide -392A>G in CYP3A4) and the CYP3A5*1/*1, CYP3A5*1/*3 and CYP3A5*3/*3 genotypes (AA, AG, and GG, respectively, at nucleotide 6986A>G in CYP3A5) were carried out by direct-sequencing using an ABI-PRISM® 3100 genetic analyzer (Applied Biosystems).

Genotyping of ABCB1 exon 21 G2677T/A (RefSNP, rs2032582) and ABCB1 exon 26 C3435T (RefSNP, rs1045642) polymorphisms. Genotyping of the ABCB1 exon 21 G2677T/A and exon 26 C3435T polymorphisms was performed using polymerase chain reaction-restrict fragment length polymorphism

Table II. Characteristics of the intent to treat (ITT) population (n=132).

Characteristics	75/60 group (n=65)	60/60 group (n=67)	P-value
Age (mean ± standard dev)	59.9±10.1	59.3±10.8	>0.05
Male/female	46/19	50/17	>0.05
Histology (ADC/SQC/LCC/NSCLC-NOS)	40/22/1/2	42/17/4/4	>0.05
ECOG PS 0-1 or 2	56/9	57/10	>0.05
Stage IIIB/IV or relapsed	6/59	7/60	>0.05
Weight loss (<5 or ≥5%)	57/8	58/9	>0.05
Subsequent treatment after first-line treatment failure			
Treatment lines[a] (mean ± standard dev)	2.8±1.5	3.1±1.7	>0.05
Use of EGFR-TKI (%)	41 (63.1)	46 (68.7)	>0.05

[a]Total number of treatment lines including first-line treatment. ADC, adenocarcinoma; SQC, squamous cell carcinoma; LCC, large-cell carcinoma; NSCLC-NOS, non-small cell carcinoma not otherwise specified; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status. The 75/60 and 60/60 groups were administered the respective amounts of docetaxel/cisplatin (mg/m^2).

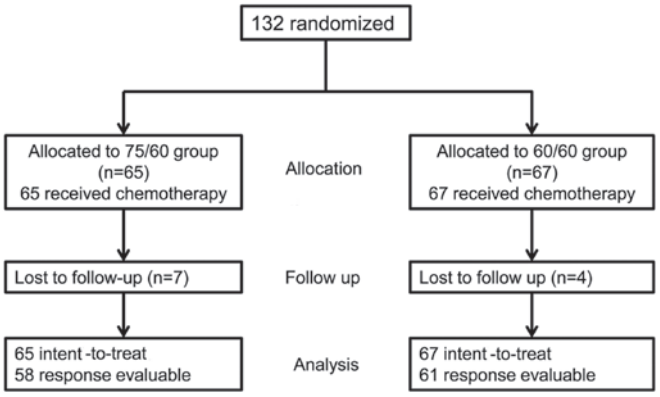

Figure 1. CONSORT diagram showing the number of patients allocated and analyzed.

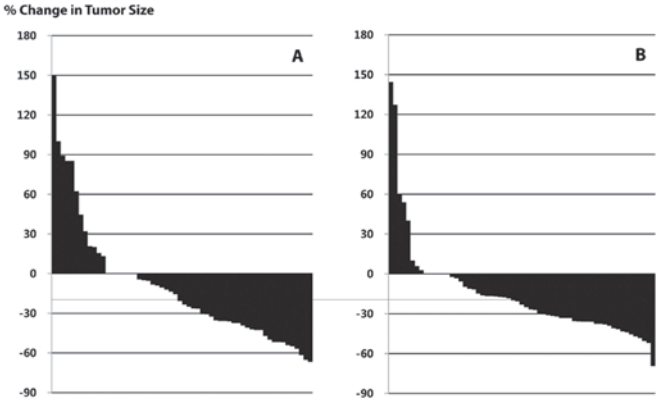

Figure 2. Waterfall plot showing the percent change of tumor diameter in response to docetaxel and cisplatin chemotherapy in (A) 75/60 and (B) 60/60 groups.

(PCR-RFLP). In brief, the PCR assay was performed in a 10-μl reaction system. The PCR products for *ABCB1 exon 21* and *exon 26* were digested by the restriction enzymes, *Rsa*I (Takara Shuzo), *Ban*I and *Sau*3AI (New England BioLabs, Inc., Ipswich, MA, USA) in a total volume of 20 μl for 3 h, 20 μl for 3 h, and 20 μl for 4 h at 37˚C. The digested products were separated on an 8% acrylamide gel. Restriction fragments were visualized after ethidium bromide staining of the acrylamide gel with the use of an ultraviolet transilluminator. Sequencing with an ABI-PRISM® 3100 genetic analyzer (Applied Biosystems) was used to confirm the PCR-RFLP results.

Results

Clinical efficacy and toxicity. From September 2007 to September 2009, 132 patients were enrolled in the study and randomized to the 75/60 (n=65) or 60/60 group (n=67) (Fig. 1). As shown in Table II, both groups were well-matched in terms of age, gender, histology, performance status, stage and weight loss. After the first-line treatment, the number of subsequent treatment lines and proportion of patients treated with epidermal growth factor tyrosine kinase inhibitor were not different between the two groups.

In the ITT population, response rates (RR) were 38.5% in the 75/60 group and 40.3% in the 60/60 group (Fig. 2 and Table III). The 95% confidence interval for the difference in response rate was -14.8 to 18.5%. Since the range was higher than the predefined non-inferiority limit, we concluded that the response rate of the 60/60 group was not inferior to the 75/60 group. There were no significant differences in the number of cycles (3.42 vs. 3.57), or progression-free survival (median, 4.9 vs. 4.7 months) between the two groups (Fig. 3A). However, the dose reduction rate (53.8 vs. 22.4%, P<0.001), and incidence of grade 3-4 neutropenia (81.3 vs. 60.3%, P=0.009) were significantly higher in the 75/60 group compared to the 60/60 group. No significant difference in overall survival was noted between the two groups (Fig. 3C).

Within the 75/60 group, dosage reductions were made for 35 patients, while no dosage modification was performed in 30 patients. Age of patients, number of delivered cycles,

Table III. Comparison of the results after treatment in the intent to treat (ITT) population.

	75/60 group (n=65)	60/60 group (n=67)	P-value
PR/SD/PD/NE	25/23/10/7	27/27/7/6	
Response rate (ITT)	38.5%	40.3%	>0.05
Response rate (RE)	43.1%	44.3%	>0.05
Relative dose intensity (mean ± standard dev)	93.8±6.2	97.9±4.1	<0.001
Dose reduction			
Yes/no (%)	35/30 (53.8)	15/52 (22.4)	<0.001
Cycles (mean ± standard dev)	3.42±1.69	3.57±1.71	>0.05
Grade 3 or 4 toxicities (%)			
Leukopenia	33/64 (51.6)	22/63 (34.9)	0.058
Neutropenia	52/64 (81.3)	38/63(60.3)	0.009
Anemia	0/52	2/47 (4.3)	>0.05
Anorexia	4/49 (8.2)	4/52 (7.7)	>0.05
Diarrhea	4/18 (22.2)	1/22 (4.5)	>0.05
Nausea/vomiting	3/20 (15.0)	4/28 (14.3)	>0.05

PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ITT, intent to treat population; RE, response evaluable population. The 75/60 and 60/60 groups were administered the respective amounts of docetaxel/cisplatin (mg/m^2).

Table IV. Comparison of the characteristics between the patients whose doses were reduced vs. those whose doses were not reduced in the 75/60 group.

	Dose reduced (n=35)	Not reduced (n=30)	P-value
Age (mean ± standard dev)	62.3±10.2	57.2±9.3	<0.05
ECOG PS 0-1/2	31/4	25/5	>0.05
PR/SD/PD/NE	21/12/2/0	4/11/8/7	
Response rate	60.0%	13.3%	<0.001
Relative dose intensity (mean ± standard dev)	89.1±4.0	99.3±2.5	<0.001
Cycles (mean ± standard dev)	4.06±1.42	2.67±1.67	<0.05

SD, stable disease. ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response; PD, progressive disease; NE, not evaluable.

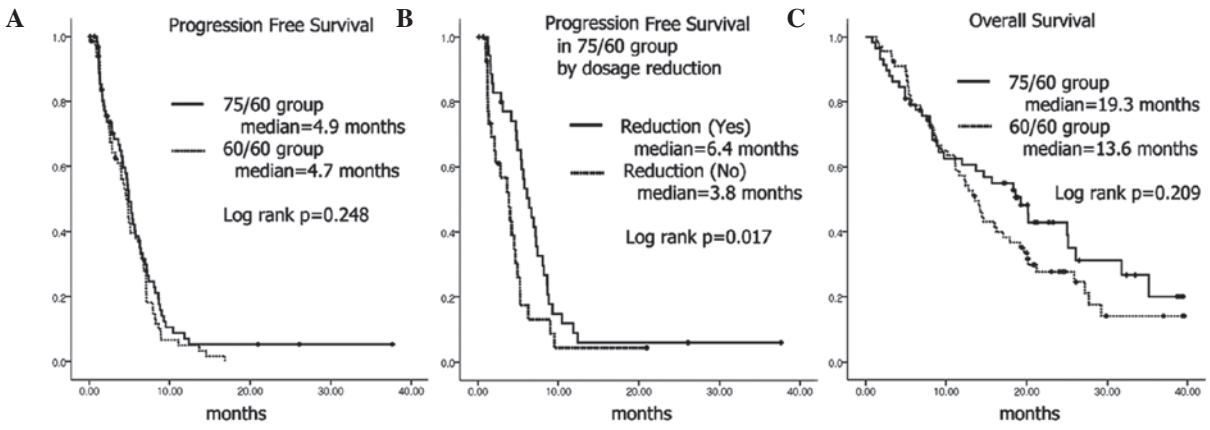

Figure 3. (A) Progression-free survival of the 75/60 and 60/60 groups. (B) Progression-free survival of the patients whose dosage was reduced or not reduced in the 75/60 group. (C) Overall survival of patients in the 75/60 and 60/60 groups. The 75/60 and 60/60 groups were administered the respective amounts of docetaxel/cisplatin (mg/m^2).

Table V. Hardy-Weinberg equilibrium for SNPs of the CYP3A5, CYP3A4 and ABCB1 genes.

CYP3A5 A6986G			CYP3A4 -392A>G			ABCB1 C3435T			ABCB1 G2677T/A		
	Obs	Exp		Obs	Exp		Obs	Exp		Obs	Exp
AA	5	5.8	AA	86	86	CC	44	40.7	GG	22	18.9
AG	35	33.4	AG	0	0	CT	31	37.6	GT	21	27.9
GG	47	47.8	GG	0	0	TT	12	8.7	TT	12	10.3
									GA	16	15.4
									TA	15	11.4
									AA	1	3.1
χ^2	0.210					χ^2	2.691		χ^2	5.137	
df	1					df	1		df	3	
P	0.647					P	0.100		P	0.162	
A	0.26		A	1		C	0.68		G	0.47	
G	0.74		G	0		T	0.32		T	0.34	
									A	0.19	

SNPs, single-nucleotide polymorphisms; Obs, observed frequencies; Exp, expected frequencies; df, degree of freedom.

Table VI. Genotypes of the CYP3A5, CYP3A4 and ABCB1 genes and hematologic toxicities.

Single-nucleotide polymorphism	Genotype	Patients with grade 3-4 neutropenia	Patients without grade 3-4 neutropenia	P-value (χ^2 test)
CYP3A5	*1/*1 (AA)	2	3	0.047
(A6986G)	*1/*3 (AG)	22	12	
	*3/*3 (GG)	38	8	
CYP3A4	*1A/*1A (AA)	62	22	
(-A392G)	*1A/*1B (AG)	0	0	
	*1B/*1B (GG)	0	0	
ABCB1	C/C	29	13	0.718
(C3435T)	C/T	24	7	
	T/T	9	3	
ABCB1	G/G	16	6	0.424
(G2677T/A)	G/T(A)	24	12	
	T(A)/T(A)	22	5	

response rate and progression-free survival were significantly higher in patients with dosage reductions compared to those whose doses were not reduced (Table IV and Fig. 3B).

Genotyping analysis. Genotyping for the CYP3A4, CYP3A5 and ABCB1 genes were performed in 87 patients. None of the observed frequencies were significantly different from expected values (Table V). Among 86 patients who were tested for a CYP3A4 polymorphism, all had the AA genotype, while other alleles of CYP3A5 and the ABCB1 gene showed certain proportions in 87 patients.

When related to hematologic toxicities, the CYP3A5 A6986G polymorphism showed a significant correlation. Patients with G alleles (non-expressing variant) showed significantly higher incidence of grade 3-4 neutropenia (Table VI). No significant correlation was found between ABCB1 and CYP3A4 genotypes, and hematologic toxicities. Haplotype analysis with CYP3A5 and ABCB1 SNPs showed no significant association with hematologic toxicities. There was also no significant correlation between genotypes and chemotherapy response.

Discussion

Lung cancer is a heterogeneous disease. In the past it was only necessary to know whether it was small-cell lung cancer or NSCLC to choose a chemotherapy regimen. Recently, we have begun using different chemotherapy regimens for squamous cell carcinoma or non-squamous cell carcinoma, even though both types are in the NSCLC category. In addition, different small-molecule inhibitors are being used based on the molecular characteristics of tumors even though they may have the same histology (13).

This personalized treatment for lung cancer requires knowledge not only of the characteristics of tumor cells but also of the individual characteristics of patients harboring the tumors. Since the pharmacokinetic or pharmacodynamic profile may vary according to individual or racial characteristics, an attempt has been made to explain most differences by SNPs.

In this study, we showed the non-inferiority of a 60 mg/m^2 dose of D compared to a 75 mg/m^2 dose of D in a Korean population, which is similar to previously published Japanese data (3). Therefore, we propose that D 60 mg/m^2 in three weekly doses, which is lower than the standard dose of D 75 mg/m^2, is optimal for East Asian populations in terms of its proven efficacy and toxicity profile.

To answer the question as to where genetic differences may arise, we used genomic DNA acquired from the subjects in this trial to study polymorphisms of CYP3A4, CYP3A5 and ABCB1 which could affect the activity of proteins dealing with D. We found that the frequencies of those three genotypes were not different from previous reports (14) which studied Asians, Caucasians and Africans. In our study, the proportion of G allele in CYP3A5 was 0.74, which has been reported as 0.69-0.78 in Asians, 0.81-0.94 in Caucasians and 0.14-0.53 in Africans. This ethnic difference suggests that the optimal dose of D for Asians and Caucasians can differ from that of Africans. In terms of different incidence of neutropenia according to the CYP3A5 genotype, we suggest that the optimal dose of D can be tailored based on this genotype.

According to our data, the incidence of toxicity and response rates did not differ according to the SNPs of CYP3A4 and ABCB1. In this study, every patient had the A allele in the CYP3A4 locus, suggesting low activity of CYP3A4. The frequency of the A allele was reported as 0.96-1.0 in Caucasians and Asians, while in a study of Africans, it was 0.3. The frequency of C allele in the ABCB1 C3435T locus was 0.68 compared to Asians and Caucasians (0.36-0.66) and Africans (0.70-0.86). In the ABCB1 G2677T/A locus, the frequency of the G allele was 0.47 in comparison to Asians and Caucasians (0.29-0.61) and Africans (0.89-0.97).

One can raise the question as to whether there was a possibility that the higher dose reduction rate in the 75/60 group decreased its efficacy. To address this issue, we compared the response rate within the 75/60 group. In 35 patients, doses of D were reduced during the course of treatment and in 23 patients doses were not reduced. Although the dose intensity was lower in the reduced group, the response rate was rather higher in patients whose dose was reduced compared to patients without dose reduction. In the 75/60 group, progression-free survival was significantly superior to the patients whose dosage was reduced compared to those without dosage reduction (Fig. 3B). This trend was consistent even in the 60/60 group. Progression-free survival tended to be longer in the dosage reduced group, although not significant. Thus, the answer to the question as to whether dose reduction reduced efficacy was negative because even in the 75/60 group, patients with dose reduction showed higher response rates and longer progression-free survival.

In conclusion, docetaxel 60 mg/m^2 with cisplatin was not inferior to docetaxel 75 mg/m^2 with cisplatin in response rate, and the lower docetaxel dose provides Korean patients with a better safety profile. Pharmacogenomic and racial differences should be considered in the next clinical trial design.

Acknowledgements

This study was supported by funding from Sanofi-Aventis Korea.

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