Xeroderma Pigmentosum Group D Haplotype Predicts for Response, Survival, and Toxicity after Platinum-Based Chemotherapy in Advanced Nonsmall Cell Lung Cancer

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BACKGROUND. The treatment of lung cancer has reached a therapeutic plateau. Several mechanisms of platinum resistance have been described, including the removal of platinum-DNA adduct by nucleotide excision repair (NER). Polymorphisms within the Xeroderma pigmentosum Group D protein (XPD), a member of the NER pathway, are associated with alterations in enzyme activity and may change sensitivity to platinum-based chemotherapy. The authors investigated the relation between XPD polymorphisms and treatment response, toxicity, and overall survival in patients who received platinum-based chemotherapy for advanced nonsmall cell lung cancer (NSCLC).

METHODS. Between 2001 and 2002, 108 patients with chemotherapy-naive, advanced NSCLC were recruited. Associations between XPD312/751 polymorphisms and XPD haplotype and treatment response, toxicity. and survival were evaluated.

RESULTS. Significant correlations were observed between XPD haplotype and Grade 4 neutropenia and overall survival together with a greater response to platinum-based chemotherapy for the XPD *A haplotype.

CONCLUSIONS. The XPD haplotype may represent a useful pharmacogenomic marker of platinum-based chemotherapy in patients with advanced NSCLC and requires prospective validation. ***Cancer*** **2006;106:2421–7.**

KEYWORDS: haplotype, nucleotide excision repair, platinum-based chemotherapy, lung cancer, XPD.

Worldwide, lung cancer is responsible for over 1 million deaths per annum and is the leading cause of cancer mortality.[1] Nonsmall cell lung cancer (NSCLC), the most common form (accounting for 85% of patients), usually is diagnosed late in the course of the disease, when surgical resection is not possible; and, despite the use of platinum-based regimens, the response to treatment and survival has reached a therapeutic plateau.[2–4] In an attempt to improve the utility of current regimens, a pharmacogenetic approach has been advocated.[5,6] The objective of this concept is to reduce the variation in how individual patients respond to medicines by tailoring therapy to their genetic make-up.[5] Platinum-based chemotherapy is the mainstay of treatment for patients with NSCLC. Unfortunately, up to 40% of patients do not respond to first-line, platinum-based chemotherapy,[4] although much is known about the potential mechanisms of platinum resistance[7–9]

Nucleotide excision repair is a major DNA repair mechanism

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implicated in platinum resistance[10] and requires many proteins to effect DNA damage recognition, excision, and repair.[11] Xeroderma pigmentosum Group D (XPD) forms part of a transcription complex (TFIIH) that plays an integral role in the nucleotide excision repair pathway that encodes an essential 5′→3′ helicase, unwinding the DNA helix prior to incision and cleavage of platinum-damaged DNA.[12] Sensitivity to alkylating agents, such as cisplatin, was related inversely to the XPD protein level in a panel of 60 human tumor cell lines from the National Cancer Institute.

Two nonsynonymous polymorphisms of the XPD gene occur: aspartic acid 312 asparagine (Asp312Asn; G→A) in exon 10 and lysine 751 glutamine (Lys751Gln; A→C) in exon 23. Significant linkage disequilibrium has been demonstrated in previous studies.[13–16] A recent meta-analysis has confirmed that XPD751Gln and XPD312Asn are risk alleles and that patients who are homozygous for each variant possess a significantly increased risk of developing lung cancer.[17] Reduced DNA repair capacity conferred by possession of the variant alleles may offer an attractive molecular model by which response to platinum-based chemotherapy may be predicted; thus, it is possible that XPD genotype may confer a differential host effect after platinum-based chemotherapy. Consequently, we sought to identify the polymorphic frequencies of the XPD loci in patients with advanced NSCLC who received platinum-based chemotherapy as part of a Phase III randomized trial and to determine the effect of these polymorphisms on toxicity, response to platinum-based chemotherapy, and survival.

MATERIALS AND METHODS

Patient Selection

Between June 2001 and November 2002, 422 patients participated in a randomized Phase III trial of docetaxel/carboplatin versus mitomycin, ifosfamide, cisplatin (MIC) or mitomycin, vinblastine, cisplatin (MVP) in patients with advanced NSCLC from 16 institutions across the United Kingdom. For patients who were recruited from 2 hospitals in South Manchester (Wythenshawe and Christie Hospitals, South Manchester, United Kingdom), additional informed consent was sought to provide a whole blood sample for genotyping. Patients who consented to this represent the genotype cohort reported herein. The local research and ethics committee approved the study. The age, stage of disease, histology, and Eastern Cooperative Oncology Group (ECOG) performance status were obtained at study entry. Follow-up information, treatment response, and survival were derived from the clinical trials data base at the Christie Hospital.

All patients who were enrolled in the study had pathologically confirmed, Mountain[18] Stage III or IV, chemotherapy-naive NSCLC with an ECOG performance status of 0 to 2 and received either docetaxel 75 mg/m^2 and carboplatin (area under the concentration time curve, 6) every 3 weeks or mitomycin C 6 mg/m^2, cisplatin 50 mg/m^2, and vinblastine 6 mg/m^2 or ifosfamide 3 g/m^2 every 3 weeks up to a maximum of 4 cycles. Tumors were required to be measurable in at least 1 dimension using the Response Evaluation Criteria in Solid Tumors.[19] Briefly, responses were determined in relation to the change in the sum of long axis dimensions (LD) for all target lesions between baseline and 4 weeks after the completion of chemotherapy. A complete response (CR) was identified if no residual disease was evident, a partial response (PR) was defined as a reduction >30% in the sum LD, progressive disease (PD) was defined as an increase >20% in the sum LD, and stable disease (SD) was defined if the criteria were not met for CR, PR, and PD. Responses were determined at the end of chemotherapy by trial investigators without prior knowledge of clinical outcome. Hematologic and nonhematologic toxicity was assessed by using the National Cancer Institute's Common Toxicity Criteria (version 2.0; January 30, 1998) and the maximum toxicity recorded for each cycle of chemotherapy administered.

DNA Extraction and Genotyping

Peripheral blood was drawn after patients were randomized and enrolled into the chemotherapy trial, and DNA was extracted from these samples using the QIAamp Blood DNA Midi Kit (Qiagen, Crawley, United Kingdom) and 2 mL of whole blood according to the manufacturer's instructions. The XPD Lys751Gln polymorphism was determined by using a modified, previously reported polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) procedure.[20] *Pst*I digestion (Promega, Madison, WI) was used for the restriction fragment analyses, and genotype was determined by using 2% agarose electrophoresis and ethidium-bromide staining. For quality control, we subjected a random 10% of samples to sequencing (using the ABI3100 capillary sequencer) to confirm the accuracy of the PCR-RFLP. Because of the increased availability of sequencing capacity during the study period, the XPD Asp312Asn polymorphism was determined by using PCR and direct sequencing, and the genotype was determined using the Phred, Phrap, PolyPhred, and Consed software packages.[21–24] PCR oligonucleotides were obtained from MWG Biotech (Milton Keynes, United Kingdom) after a BLASTN

TABLE 1
Polymerase Chain Reaction and Sequencing Primers for Xeroderma Pigmentosum Group D Polymorphisms

XPD Polymorphism	Primer Sequence	Temperature (°C)
Asp312Asn (exon 10)	F: GAGTACCGGCGTCTGGTGGA	60
	R: TGCGAGGAGACGCTATCAGC	
	S: GGCTGCGGGAGGCCAGCG	
Lys751Gln (exon 22)	F: GCCCGCTCTGGATTATACG	60
	R: CTATCATCTCCTGGCCCCC	
	S: GGATTATACGGACATCTCCAA	

XPD: Xeroderma pigmentosum Group D; Asp: aspartic acid; Asn: asparagine; Lys: lysine; Gln: glutamine; F: 5′ to 3′ forward primer; R: 3′ to 5′ reverse primer; S: sequencing primer.

TABLE 2
Genotype and Allele Frequencies for Xeroderma Pigmentosum Group D Polymorphisms in Advanced Nonsmall Cell Lung Cancer

	Genotype (Allele Frequency)*	
Genotype	Asp312Asn (G→A) (*N* = 97)	Lys751Gln (A→C) (*N* = 99)
Wild type	GG (39)	AA (40)
Heterozygote	GA (50)	AC (47)
Homozygous variant	AA (11)	CC (13)
Allele frequency	G (0.639)	A (0.636)
	A (0.361)	C (0.364)

Asp: aspartic acid; Asn: asparagine; Lys: lysine; Gln: glutamine;
* There were no significant differences between observed and expected frequencies (chi-square test; $P<.05$).

search to ensure 100% sequence homology with the gene of interest (accession no. AY092780). Oligonucleotide sequences and annealing temperatures are listed in Table 1, and 35 PCR cycles were used. XPD haplotypes were assigned according to the following annotation: Asp312(G)/Lys751(A), *A; Asn312(A)/Gln751(C), *B; Asn312(A)/Lys751(A), *C; and Asp312(G)/Gln751(C), *D.

Statistical Analysis

The XPD polymorphisms were analyzed according to haplotype. The objective of the analysis was to determine the association between the polymorphisms and demographics, pretreatment characteristics, and outcome data (treatment response, survival, and hematologic toxicity). Patients' baseline and pretreatment characteristics, toxicity, and responses were summarized by groups.

Pearson chi-square tests were used to determine the relation between each categorical variable and XPD genotype/haplotype. Survival was calculated as the time from the date of pathologic confirmation until death from any cause or until last review. Hazard ratios for survival, together with their 95% confidence intervals (95%CI), were calculated by using Cox proportional hazards regression for haplotype, histologic subgroup, performance status, and disease stage. Differences in survival according to haplotype and the additional prognostic groups were compared by using the Kaplan–Meier method and log-rank tests. The Kruskal–Wallis test was used to determine toxicity of treatment according to XPD genotype. All statistical tests were 2-sided and were performed by using SPSSX for Windows software (version 10.1).

RESULTS

Trial Demographics and Genetic Frequencies

One hundred eight patients participated in the study and provided whole blood for genotyping. No statistically significant differences in age, gender, histology, disease stage, or performance status were demonstrated between the 2 chemotherapy arms for the cohort.

The genotype cohort consisted of 74 males (68.5%) and 34 females (31.5%) with a median age 62.5 years (range, 35-80 years). No statistically significant differences in response to chemotherapy were observed between the 2 chemotherapy arms. Overall, an objective response was observed in 33.6% of patients, SD was observed in 30.6% of patients, and PD was observed in 35.7% of patients. The median overall survival was 282 days (95%CI, 221-343 days). Genotypes demonstrated linkage disequilibrium, and haplotypes were defined as XPD *A through *D. The XPD751 genotype could be determined in 99 patients, and the XPD312 genotype could be determined in 97 patients. Therefore, the XPD haplotype was available in 97 patients: Response data were available for 89 patients, 87 patients, and 87 patients, respectively. The genotype, haplotype, and allele frequencies for the genotype cohort are listed in Tables 2 and 3.

Genotype and Tumor Response

XPD haplotype was associated with response to platinum-based chemotherapy. Patients with XPD *A/*A demonstrated a greater response to chemotherapy (40%) compared with patients who had ≥1 XPD *B allele (haplotype: *A/*B, 35.3%; *B/*B, 22.2%). Similarly, the rates of PD increased with the XPD *B allele (haplotype: *A/*A, 30%; *A/*B, 29.4%; *B/*B, 44.4%). The small number of patients with the XPD *C and XPD *D alleles precluded a definitive assessment of their effect on treatment response, but it is noteworthy that this group demonstrated a response to chemotherapy similar to that achieved among patients with the XPD *B/B haplotype (Table 4).

TABLE 3
Haplotype Distributions of the *XPD* Gene in Patients with Advanced Nonsmall Cell Lung Cancer

Variable	Haplotype	Frequency (N = 97)
Genotype 312/751		
Wt/Wt	AA	32
Wt/Het	AD	6
Wt/Var	DD	0
Het/Wt	AC	7
Het/Het	AB	38
Het/Var	BD	3
Var/Wt	CC	1
Var/Het	BC	1
Var/Var	BB	9
Haplotype frequency†		
*A		0.593
*B		0.309
*C		0.052
*D		0.046

Wt: wild type; Het: heterozygote; Var: homozygote variant; *A: aspartic acid (Asp)312(G)/lysine (Lys)751(A); *B: asparagine (Asn)312(A)/glutamine (Gln)751(C); *C: Asn312(A)/Lys751(A); *D: Asp312(G)/Gln751(C).
† There were no significant differences between observed and expected frequencies (chi-square test; P<.05).

TABLE 4
Xeroderma Pigmentosum Group D Genotype, Haplotype, and Tumor Response

Variable	Percentage of Patients (No.)		
	Objective Response	Stable Disease	Progressive Disease
Trial cohort (n = 422)	30.6	28.9	26.3
Genotype cohort (n = 98)	33.6 (33)	30.6 (30)	35.7 (35)
XPD haplotype (n = 87; P = .80)			
XPD *A/*A (n = 30)	40.0 (12)	30.0 (9)	30.0 (9)
XPD *A/*B (n = 34)	35.3 (12)	35.3 (12)	29.4 (10)
XPD *B/*B (n = 9)	22.2 (2)	33.3 (3)	44.4 (4)
Other (n = 14)	28.6 (4)	21.4 (3)	50.0 (7)
XPD751 genotype (n = 89; P = .83)			
Wild type Lys/Lys (n = 36)	38.9 (14)	30.6 (11)	30.6 (11)
Heterozygote Lys/Gln (n = 40)	32.5 (13)	35.0 (14)	32.5 (13)
Variant Gln/Gln (n = 13)	30.8 (4)	23.1 (3)	46.2 (6)
XPD312 genotype (n = 87; P = .99)			
Wild type Asp/Asp (n = 34)	35.3 (12)	29.4% (10)	35.3 (12)
Heterozygote Asp/Asn (n = 42)	35.7 (15)	31.0% (13)	33.3 (14)
Variant Asn/Asn (n = 11)	27.3 (3)	36.4% (4)	36.4 (4)

XPD: Xeroderma pigmentosum Group D; *A: aspartic acid (Asp)312(G)/lysine (Lys)751(A); *B: asparagine (Asn)312(A)/glutamine (Gln)751(C).

Toxicity and Genotypes

No significant association was demonstrated between XPD haplotype and nonhematologic toxicity. For hematologic toxicity, grade of neutropenia demonstrated a significant correlation with XPD haplotype, such that the XPD *A allele was associated with greater Grade 4 neutropenia compared with XPD *B (haplotype: *A/*A, 49.9%; *B/*B, 33.3%; P = .05) (Table 5). No significant association was demonstrated between XPD haplotype and anemia and/or thrombocytopenia.

TABLE 5
Common Toxicity Criteria for Neutropenia by Xeroderma Pigmentosum Group D Haplotype in Patients with Advanced Nonsmall Cell Lung Cancer who Received Platinum-Based Chemotherapy

Haplotype (N = 87)	CTC Grade for Neutropenia: Percent of Patients					P value
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
*A/*A	9.4	9.4	12.5	21.9	46.9	
*A/*B	2.8	8.3	8.3	5.6	75	
*B/*B	33.3	0	11.1	22.2	33.3	.05

CTC: Common Toxicity Criteria; *A: aspartic acid 312(G)/lysine 751(A); *B: asparagine 312 (A)/glutamine 751 (C).

Genotype and Survival

No significant correlation with survival was observed for age, histology, performance status, or disease stage (Table 6). The overall median survival was 282 days (95%CI, 221-343 days). However, significant differences in median survival were demonstrated according to XPD haplotype (Fig. 1). Patients with the XPD *A/*A haplotype had a median survival of 388 days (95%CI, 214-562 days) compared with 176 days (95%CI, 102-250 days) for patients with the XPD *B/*B haplotype. One-year survival was >50% for patients with XPD *A/A and <20% for patients with XPD *B/B. No patient who had the XPD *B/B genotype survived beyond 2 years. Patients who had homozygosity for the XPD *B allele experienced a 2.7-fold reduction in the rate of survival compared with patients who had homozygosity for the XPD *A after platinum-based chemotherapy.

DISCUSSION

Single nucleotide polymorphisms (SNPs) account for >90% of genetic variation within the human genome.[6] With the completion of the Human Genome Project, >1.42 million SNPs have been described and validated,[25] which, together with the currently available technology, may make pretreatment patient genotyping an affordable prospect.[26,27] Nonetheless, this requires the demonstration that a particular genotype is associated with response to treatment and altered survival.

In view of the current therapeutic plateau in treat-

TABLE 6
Meroderma Pigmentosum Group D Genotype and Survival

Characteristic	Median Survival (Days)	95%CI	*P* Value	HR	95%CI	*P* Value
Trial Cohort						
Docetaxel/carboplatin	388	170–606		1.00		
MIC/MVP	265	221–308	.34	1.29	0.76–2.21	.35
Histology						
Squamous	265	229–301		1.00		
Adenocarcinoma	336	196–476		0.92	0.48–1.75	
Large cell	282	49–515	.80	0.80	0.42–1.54	.80
ECOG PS						
0/1	279	219–339		1.00		
2	Undefined		.66	0.86	0.42–1.71	.66
Stage						
IIIA	361	251–471		1.00		
IIIB	270	216–324		1.42	0.64–3.20	
IV	279	188–370	.68	1.25	0.64–2.46	.68
Genotype cohort	282	221–343				
Haplotype						
*A/*A	388	214–562		1.00		
*A/*B	336	92–580		0.86	0.42–1.74	
*B/*B	176	102–250	.036	2.77	1.06–7.24	.049

HR: hazard ratio; 95%CI: 95% confidence interval; MIC: mitomycin, ifosfamide, and cisplatin; MVP: mitomycin, vinblastine, and cisplatin; ECOG PS: Eastern Cooperative Oncology Group performance status; *A: aspartic acid 312 (G)/lysine 751 (A); *B: asparagine 312 (A)/glutamine 751 (C).

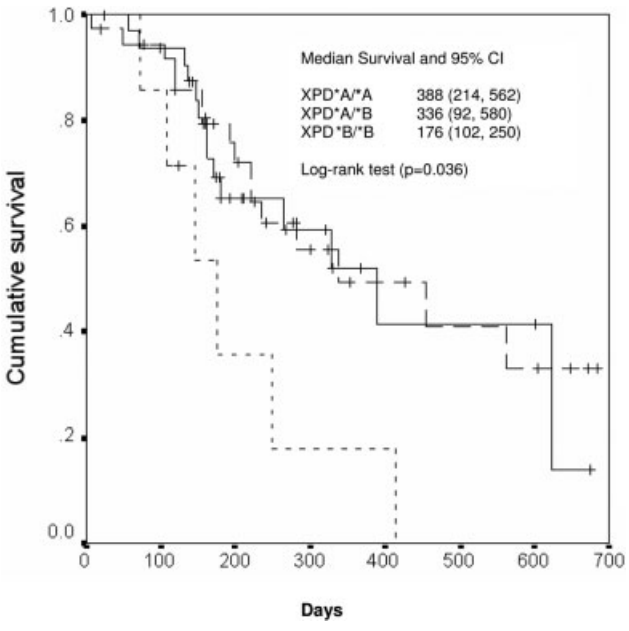

FIGURE 1. Kaplan–Meier survival curves are shown for patients with advanced nonsmall cell lung cancer who received platinum-based chemotherapy according to Xeroderma pigmentosum Group D (XPD) haplotype. Short dashed line: *B/*B; long dashed line: *A/*B; solid line: *A/*A. 95%CI: 95% confidence interval.

ment for patients with advanced NSCLC, we evaluated whether nonsynonymous polymorphisms in genes associated with platinum resistance were capable of predicting response to chemotherapy and influencing survival after platinum-based chemotherapy. We have demonstrated that XPD haplotypes are associated with response to platinum-based chemotherapy and are associated significantly with Grade 4 neutropenia and overall survival in patients with advanced NSCLC.

Several authors have investigated the impact of XPD polymorphisms on outcomes after chemotherapy and have demonstrated conflicting evidence with regard to the effect of individual XPD genotypes Asp312Asn and Lys751Gln. Park et al. reported the outcome of 73 patients with pre-treated metastatic colorectal cancer receiving oxaliplatin and 5-flurouracil chemotherapy according to both the Lys751Gln and Asp312Asn alleles. A significant objective response to chemotherapy was noted in favor of the Lys751Lys genotype ($P = .015$) together with a higher rate of PD (≈50%; $P = .008$) for patients with the Gln751Gln genotype, although no such association was observed for the XPD312 genotypes. The median survival was affected significantly by genotypes for XPD751, with the wild-type genotype demonstrating superior survival (17.4 months for patients with Lys751Lys, 12.8 months for patients with Lys751Gln, and 3.3 months for patients with Gln751Gln; $P = .002$).[13] Extended data on 106 patients continued

to demonstrate a survival advantage for the wild-type allele (wild-type, 528 days; heterozygote, 255 days; homozygote variant, 183 days; $P = .03$).[28] In a subsequent multivariate analysis of numerous DNA repair and drug metabolism gene polymorphisms, the homozygote variant genotype Gln751Gln increased the relative risk of dying by 2.44-fold ($P = .049$) and increased the risk of PD by 1.25-fold ($P = .76$). In addition, the Lys751Lys genotype was 1 of 4 favorable polymorphisms that was capable of predicting survival in response to platinum-based chemotherapy ($P<.001$).[29] Gurubhagavatula et al. retrospectively studied 103 patients with advanced NSCLC who received platinum-based combination chemotherapy, and they reported an overall median survival of 14.9 months. In that study, the Asp312Asn polymorphism was identified as a prognostic marker, and the homozygote variant genotype was associated with significantly inferior survival (Asp/Asp, 16.3 months; Asp/Asn, 15.2 months; Asn/Asn, 6.6 months; $P = .003$). No data were offered in that study with respect to treatment response.[30] In the only other published study that examined treatment response and survival according to XPD genotype, no firm conclusions could be drawn because of the absence of the homozygous variant genotypes in Korean patients with NSCLC.30

The majority of patients in our cohort demonstrated either LysLys/AspAsp (34%), LysGln/AspAsn (39%), or GlnGln/AsnAsn (8%) genotypes. Because of the strong linkage disequilibrium between the 2 polymorphisms, which also has been observed in other studies,[14–16,31] we defined haplotypes according to the XPD312 and XPD751 genotypes and considered their effect on treatment response, toxicity, and survival for these groups. This report represents one of the largest series in advanced NSCLC evaluating a pharmacogenomic approach to therapy. XPD haplotypes represent potentially useful biomarkers for the predictive prescription of platinum-based chemotherapy and require prospective evaluation. The data suggest that XPD haplotypes may be useful pharmacogenomic markers for determining response and clinically important toxicity to platinum-based chemotherapy and predictors of overall survival. The current findings also call into question whether patients who have the XPD *B/*B haplotype should receive platinum-based chemotherapy.

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