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Polymorphisms in DNA repair genes and therapeutic outcomes of AML patients from SWOG clinical trials

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Repair of damage to DNA resulting from chemotherapy may influence drug toxicity and survival in response to treatment. We evaluated the role of polymorphisms in DNA repair genes *APE1*, *XRCC1*, *ERCC1*, *XPD*, and *XRCC3* in predicting therapeutic outcomes of older adults with acute myeloid leukemia (AML) from 2 Southwest Oncology Group (SWOG) clinical trials. All patients received standard chemotherapy induction regimens. Using logistic and proportional hazards regression models, relationships between genotypes, haplotypes, and toxicities, response to induction therapy, and overall survival were evaluated. Patients with *XPD* Gln751C/Asp312G ('D') haplotype were more likely to have complete response (OR = 3.06; 95% CI, 1.44-6.70) and less likely to have resistant disease (OR = 0.32; 95%CI, 0.14-0.72) than patients with other haplotypes. *ERCC1* polymorphisms were significantly associated with lung (*P* = .037) and metabolic (*P* = .041) toxicities, and patients with the *XRCC3* 241Met variant had reduced risk of liver toxicity (OR = 0.32; 95%CI, 0.11-0.95). Significant associations with other toxicities were also found for variant *XPD* genotypes/haplotypes. These data from clinical trials of older patients treated for AML indicate that variants in DNA repair pathways may have an impact on both outcomes of patients and toxicities associated with treatments. With validation of results in larger samples, these findings could lead to optimizing individual chemotherapy options. (Blood. 2007;109:3936-3944)

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Introduction

Acute myeloid leukemia (AML) is not the most common cancer in the United States or worldwide, but survival rates are poor and not improving. Among adults with AML, less than 20% of patients are living 5 years after the initial diagnosis. Despite recent scientific advances in understanding the molecular biology of AML and mechanisms of multidrug resistance (MDR), the targets for new successful therapeutic interventions are still waiting to be discovered. The identification of individuals who would not benefit from aggressive chemotherapy regimens and, thus, could be spared the risk of treatment-related mortality, requires more knowledge from pharmacogenetic studies. The latter strategy is especially important for elderly patients, who comprise the major age category for AML and whose capability to endure intensive treatment is often limited.

It has been previously noted that older patients with AML often have more cytogenetic abnormalities than younger patients and display MDR phenotype.[1] MDR phenomenon is usually responsible for cancer recurrence and treatment failures. However, evidence also suggests that increased activity of DNA repair mechanisms may contribute to worse clinical response, through repair of damage resulting from therapeutic agents, leading to a failure of the elimination of malignant clones.[2-5]

Chemotherapeutic drugs including topoisomerase I and II inhibitors, alkylating agents, and antimetabolites are capable of inducing DNA strand breaks.[6-10] Variabilities in DNA repair rates and genotoxic damage, measured by single-strand breaks and chromosomal aberrations, have been shown to be associated with DNA repair polymorphisms,[11] particularly for *XRCC1* Arg399Gln and *XPD*, exon 23. Higher sensitivity to ionizing radiation and prolonged cell-cycle delays were also associated with *APE1* 148Glu and *XRCC1* 399Gln genotypic variants.[12] Functional DNA repair capacity was previously reported to be significantly deficient in *XRCC1* 399Gln, *XRCC3* 241Met and *XPD* 312Asn, 751Gln variant allele carriers[13,14]; however, the ability to repair DNA damage was also modified by environmental exposures. One of the plausible mechanisms of action of cytosine arabinoside and anthracyclines, primary drugs used in standard treatment regimens for AML, is induction of single- and double-strand breaks (DSBs) and other DNA lesions. Thus, inherited variability in certain DNA repair pathways may modify the effects of cancer treatment with those agents.

Damage caused to DNA by various agents must be repaired to maintain genomic stability of a cell. Studies have noted associations between risk of de novo AML and DNA repair gene polymorphisms.[15,16] Increased risk of therapy-related AML was also linked to several gene polymorphisms in base excision repair (BER; *XRCC1* Arg399Gln), nucleotide excision repair (NER; *XPD* Lys751Gln), and DSB repair (*RAD51* G135C and *XRCC3*

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Thr241Met) pathways,[15,17,18] and may be linked to secondary AML etiology through failure to recognize or excise accumulated DNA lesions. Although several published reports now exist on associations between polymorphisms in DNA repair genes and cancer risk,[19-22] fewer studies have been conducted to evaluate relationships between DNA repair gene polymorphisms and response to treatment. Studies of lung cancer[23-27] and colorectal carcinoma[28-30] noted significant differences in overall survival by polymorphisms in DNA repair enzymes, with an indication that poorer survival was linked to increased DNA repair. In a recent study of AML, poorer prognosis was associated with a polymorphism in *XPD*, which participates in the NER pathway.[18] Despite the fact that numerous associations have been found between toxicity profiles of patients and polymorphisms in drug-metabolizing enzymes,[31-33] few data are available on the impact of DNA repair gene polymorphisms on treatment-related toxicity.[34-36]

To evaluate the role of variants in DNA repair genes in predicting therapeutic outcomes, we assessed potential associations between complete remission (CR), resistant disease (RD), overall survival (OS) rates, and toxicity profiles and polymorphisms in BER (*APE1* (Asp148Glu), *XRCC1* (Arg399Gln)), DSB repair (*XRCC3* (Thr241Met)), and NER (*ERCC1* (IVS5 + 34C > A), *XPD/ERCC2* (Lys751Gln and Asp312Asn)) pathways among 200 patients who were enrolled in Southwest Oncology Group (SWOG) clinical trials for treatment of AML.

Patients, materials, and methods

Patients

These analyses included adult patients with previously untreated AML who entered either of 2 SWOG phase 3 randomized trials during November 1991 through December 1998.[37,38] Patients were accrued from 66 participating centers treating cancer patients. For both trials, eligible patients had established diagnoses of de novo or secondary AML excluding M3-FAB variant and blast crisis of chronic myeloid leukemia (CML), were at least 56 years old, and met minimum liver, kidney, and cardiac function criteria. Patients on SWOG-9031 received remission induction chemotherapy with daunorubicin (45mg/m^2/d for 3 days) and standard-dose cytosine arabinoside (200mg/m^2/d for 7 days) with or without recombinant human granulocyte colony-stimulating factor (rhG-CSF). Patients on SWOG-9333 received induction either with the same ARA-C/DNR induction regimen (AD), or with mitoxantrone and etoposide (ME), with addition of granulocyte-macrophage CSF (GM-CSF) on remission achievement only. Since the ME arm had somewhat poorer treatment outcomes,[37] only SWOG-9333 patients in the AD arm were included in the present study. All AD patients who met the eligibility criteria of their respective trials and had sufficient volumes of cryopreserved marrow or blood cells in the SWOG Myeloid Repository were included in this study.

Patients provided samples for research after informed consent was given, in accordance with the Declaration of Helsinki. The parent trials were approved by the institutional review boards and included permission for samples to be used for future analyses. This study was deemed exempt by the Roswell Park Cancer Institute Institutional Review Board because we received only anonymous samples for genotyping. All genotyping was performed at BioServe Biotechnologies (Laurel, MD) and all statistical analyses were performed by SWOG statisticians. No part of this study was ever open at Roswell Park Cancer Institute; results were provided to us by the SWOG statistician.

Genotyping

DNA was extracted from bone marrow samples and genotyped for SNPs in *APE1* (rs3136820), *XRCC1* (rs25487), *ERCC1* (rs3212961), *XPD/ERCC2* (rs13181 and rs1799793), and *XRCC3* (rs861539), using matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS). Duplicate aliquots for approximately 10% of the samples were randomly distributed throughout the plates for quality control purposes. Controls for genotype and 2 'no template' controls were also included on each plate. All genotyping results were reviewed manually for quality control. Five polymorphisms, excluding the one in *ERCC1*, were nonsynonymous, resulting in amino acid changes. The *ERCC1* SNP occurs in the intronic part of the gene.

Statistical analysis

Data regarding patient and disease characteristics, treatment outcomes, and toxicities were collected and subjected to quality review according to standard practices of SWOG. Data analysis was performed using SAS 8.0 software (SAS Institute, Cary, NC). χ^2 tests and Fisher exact test were used to evaluate associations between genotypes and haplotypes and categorical variables (sex, race, de novo versus secondary AML onset, and FAB class). Associations of genotypes and haplotypes with continuous variables such as age, white blood cell (WBC) count, and bone marrow and peripheral blast percentages were analyzed using ANOVA and Kruskal-Wallis tests. χ^2 test statistics with 1 degree of freedom were used to test for deviation from Hardy-Weinberg equilibrium (HWE) in each polymorphism. Estimation haplotype (EH) genetic linkage utility program was used to evaluate possible linkage disequilibrium (LD) for the SNPs located in close proximity to each other. Associations between genotypes and haplotypes and therapeutic outcomes were analyzed using logistic regression models for CR and RD following induction chemotherapy, and using proportional hazards regression models for OS. Multivariate regression models were used to investigate differences between genotypes and haplotypes after adjusting for the effects of other prognostic factors (age, cytogenetic risk group, AML onset, and peripheral blast percentage). For analysis of toxicities, the following categories were created by combining specific toxicities defined by the SWOG toxicity criteria for SWOG-9031[39] and the Common Toxicity Criteria (CTC) version 2.0 (National Cancer Institute [NCI, Bethesda, MD) for SWOG-9333: lung, liver, metabolic, gastrointestinal (GI), and genitourinary (GU). Because a patient may have had multiple occurrences of a given toxicity, each patient's maximum grade for each specific toxicity category was used for analysis. For each gene and each organ group, polychotomous logistic regression analyses were run to test whether the distributions of highest toxicity grade varied among genotypes (each of these analyses excluded patients with toxicities of only unknown grade). These analyses treat each patient's maximum grade of a given type of toxicity as an ordinal response variable. The estimated odds ratio (OR) represents the odds, relative to the referent genotype, of having toxicity above any given grade, averaged over all grades. For example, OR = 2 implies that the genotype of interest confers twice the risk of toxicity above any particular grade, compared to the referent genotype.

Results

A total of 372 patients were registered on SWOG-9031 (n = 211) or the AD arm of SWOG-9333 (n = 161), and 201 of these (SWOG-9031: 89; SWOG-933: 112) met the criteria for inclusion in this analysis, although one SWOG-9031 patient was not analyzed. As shown in Table 1, the patient population was almost equally distributed by sex and the majority (87%) were white. The median age was 68 years, reflecting the lower age limit of 56 for study eligibility. Forty-three (23%) of the 200 patients had AML that was secondary to prior myelodysplastic syndrome (MDS) or leukemogenic exposure. Overall patient genotype and haplotype distributions, as well as by de novo versus therapy-related AML, are displayed in Table 2. Genotypes for *XRCC1*, *XRCC3, ERCC1*, and *XPD* were in HWE. However, distribution of *APE1* genotypes departed from HWE (P = .012), with smaller numbers of heterozygotes and slight excess in both homozygote variants. This disequilibrium could be explained by the larger number of missing values

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Table 1. Summary of selected patient and disease characteristics

Characteristic	Value
Sex, no. (%)	
Female	90 (45)
Male	110 (55)
Race/ethnicity, no. (%)	
Asian	4 (2)
Black	21 (11)
White, Hispanic	5 (3)
White, non-Hispanic	169 (85)
Hispanic, NOS	1 (1)
AML onset, no. (%)	
De novo	157 (79)
Secondary	43 (22)
Favorable cytogenetics	9 (5)
Risk group, no. (%)	
Intermediate	106 (53)
Unfavorable	39 (20)
Unknown	46 (23)
FAB class, local diagnosis, no. (%)	
M0	10 (5)
M1*	48 (24)
M2	63 (32)
M3	1 (1)
M4	51 (26)
M5	19 (10)
M6	1 (1)
M7	2 (1)
Other AML	5 (3)
Age, median y (min-max)	68 (56-88)
Marrow blasts, % (min-max)	70 (10-99)
WBC count, $\times 10^9$ (min-max)	35 (0.7-298)
Peripheral blasts, %, (min-max)	75 (0-99)

NOS indicates not otherwise specified; min-max, minimum-maximum.

*One patient (141020) had local diagnosis of myelodysplastic syndrome-refractory anemia with excess blasts but central review diagnosis of AML-M1 is included as AML-M1 in this analysis.

of genotype information for this polymorphism (22 cases) or slight differences in allele frequencies among the chosen patient population. The 2 *XPD* genotypes were in high LD with each other ($P < .001$), and further analysis using *XPD* haplotypes was performed. There were no significant associations between patient or disease characteristics, including AML onset, genotype for any of the 5 genes or *XPD* haplotype, based on the χ^2 test for independence (Table 2). For this reason, and due to statistical power limitations, the analyses relating genotype and haplotype polymorphisms and therapeutic outcomes were not stratified by AML onset.

Of the 200 patients, 86 (43%) achieved CR and 65 (33%) had RD. The remaining 49 patients died before marrow recovery or adequate assessment of response. Patient characteristics that were significantly prognostic for therapeutic outcomes have been previously described.[37,38,40] Of the 200 patients included in this analysis, 185 have died. The remaining 15 patients were last known to be alive between 22 months and 10.9 years after entering their respective studies (median, 6.3 years).

Regression analysis of treatment outcomes

Associations between DNA repair gene polymorphisms and treatment outcomes (CR, RD, and OS), adjusted for covariates (age, cytogenetic risk group, AML onset, peripheral blast percentage) are shown in Table 3. There were no significant associations between any of the genotypes and CR rate. However, patients carrying one or both *XPD* 751 variant Gln alleles had significantly reduced risk of developing RD in response to induction course of chemotherapy (OR = 0.39; 95%CI, 0.17-0.83). Decreased risk of borderline significance for RD was also observed among individuals with heterozygote GA genotype of *XPD* Asp312Asn SNP (Table 3). Poorer OS was noted for the small group of patients (n = 19) with variant AA genotype of *XPD* Asp312Asn polymorphism (OR = 2.31; 95% CI, 1.19-4.49). Only 4 (25%) of the 16 *XRCC1* AA carriers achieved CR, which was markedly lower than for those with the referent GG genotype (OR = 0.27; 95% CI, 0.05-0.99), though of borderline significance. Given the large number of comparisons between genotypes and treatment outcomes that were made, this was not interpreted as strong evidence of an association. Similarly, there was a suggestion of worse OS for *ERCC1* AA carriers (hazard ratio [HR] = 2.04; 95% CI, 0.74-5.62 compared to the referent CC genotype); however, all 4 patients with the AA genotype died within 8 months of starting treatment, resulting in wide HR confidence intervals.

Associations between *XPD* haplotypes and treatment outcomes (CR, RD, and OS) are displayed in Table 4. CR rates varied significantly among the 7 haplotypes ($P = .036$), primarily due to the high CR rate in patients with DA haplotypes (73%). In analyses that adjusted for significant covariates (age, cytogenetic risk group,

Table 2. Distribution of patients' DNA repair genotypes/haplotypes by AML onset

Gene polymorphism	P†	AML onset: De novo	AML onset: Secondary	Overall no. (%)
***APE1* Asp148Glu**	.51			
GG*		43	9	52 (29.21)
GT		54	19	73 (41.01)
TT		42	11	53 (29.78)
***XRCC1* Arg399Gln**	.54			
GG		73	18	91 (46.91)
GA		68	19	87 (44.85)
AA		11	5	16 (8.25)
***XRCC3* Thr241Met**	.31			
CC		71	23	94 (50.81)
CT		59	16	75 (40.54)
TT		15	1	16 (8.65)
***ERCC1* IVS5+34C>A**	.58			
CC		119	30	149 (74.87)
CA		34	12	46 (23.12)
AA		3	1	4 (2.01)
***XPD* Lys751Gln**	.18			
AA		63	23	86 (43.65)
AC		71	13	84 (42.64)
CC		20	7	27 (13.71)
***XPD* Asp312Asn**	.75			
GG		74	21	95 (49.22)
GA		64	15	79 (40.93)
AA		14	5	19 (9.84)
XPD* haplotype	.60			
AA		54	18	72 (37.70)
AC		7	4	11 (5.76)
BB		9	4	13 (6.81)
BC		5	1	6 (3.14)
DA		19	3	22 (11.52)
DB		11	2	13 (6.81)
DC		45	9	54 (28.27)

GG genotype is the most common among whites (data obtained through NCBI SNP database).

*Haplotypes: A, Lys751A/Asp312G; B, Gln751C/Asn312A; C, Lys751A/Asn312A; D, Gln751C/Asp312G. Haplotype frequencies: A, 0.463; B, 0.117; C, 0.186; D, 0.233.

†*P* values are for comparison of de novo and secondary AML onset values.

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Table 3. Analyses of treatment outcomes by DNA repair genotypes

		CR			RD			OS		
Polymorphism	Total no.	No.	OR	CI	No.	OR	CI	No. of deaths	HR	CI
***APE1* Asp148Glu**										
GG	51	21	1.00		14	1.00	NA	46	1.00	NA
GT	68	27	0.93	0.41-2.13	29	2.08	0.90-4.98	63	0.97	0.66-1.43
TT	53	22	1.13	0.46-2.79	17	0.90	0.34-2.33	50	0.96	0.64-1.45
GT or TT	121	49	1.00	0.48-2.14	46	1.49	0.70-3.30	113	0.96	0.68-1.37
Total	172	70	NA	NA	60	NA	NA	159	NA	NA
***XRCC1* Arg399Gln**										
GG*	88	40	1.00		31	1.00	NA	81	1.00	NA
GA	83	38	0.91	0.47-1.77	24	0.87	0.44-1.73	78	1.12	0.82-1.54
AA	16	4	0.27	0.05-0.99	5	0.85	0.24-2.75	15	1.54	0.86-2.74
GA or AA	99	42	0.76	0.40-1.44	29	0.87	0.45-1.67	93	1.17	0.86-1.59
Total	187	82	NA	NA	60	NA	NA	174	NA	NA
***XRCC3* Thr241Met**										
CC*	89	35	1.00	NA	35	1.00	NA	85	1.00	NA
CT	74	30	0.84	0.41-1.70	22	0.68	0.33-1.36	66	0.90	0.65-1.25
TT	15	8	1.90	0.54-6.95	4	0.67	0.16-2.33	13	0.83	0.46-1.50
CT or TT	89	38	0.97	0.50-1.89	26	0.68	0.35-1.32	79	0.89	0.65-1.21
Total	178	73	NA	NA	61	NA	NA	164	NA	NA
***ERCC1* IVS5+34C>A**										
CC*	143	60	1.00	NA	48	1.00	NA	131	1.00	NA
CA	45	22	1.57	0.75-3.35	12	0.59	0.26-1.30	43	1.08	0.75-1.56
AA	4	1	0.50	0.02-4.27	2	1.51	0.16-14.28	4	2.04	0.74-5.62
CA or AA	49	23	1.43	0.6-2.97	14	0.65	0.29-1.38	47	1.13	0.79-1.60
Total	192	83	NA	NA	62	NA	NA	178	NA	NA
***XPD* Lys751Gln**										
AA	86	31	1.00		37	1.00	NA	80	1.00	NA
AC	84	43	1.97	0.91-4.37	21	0.43	0.18-0.96	77	0.95	0.66-1.36
CC	27	11	1.57	0.44-5.53	6	0.24	0.05-0.97	25	1.04	0.58-1.87
AC or CC	111	54	1.89	0.90-4.01	27	0.39	0.17-0.83	102	0.97	0.68-1.36
Total	197	85	NA	NA	64	NA	NA	182	NA	NA
***XPD* Asp312Asn**										
GG	95	42	1.00		39	1.00	NA	88	1.00	NA
GA	79	34	1.50	0.70-3.26	19	0.44	0.19-1.00	73	1.00	0.70-1.44
AA	19	6	0.31	0.05-1.43	6	1.04	0.24-4.21	18	2.31	1.19-4.49
GA or AA	98	40	1.20	0.58-2.51	25	0.52	0.24-1.11	91	1.11	0.79-1.57
Total	193	82	NA	NA	64	NA	NA	179	NA	NA

Estimates of ORs and HRs are adjusted for the following covariates: age (continuous), AML onset (de novo versus secondary), cytogenetic group (favorable, intermediate, unfavorable, unknown), peripheral blast percentage (continuous, unknown for 7 patients who are excluded from multivariate analyses).

NA indicates not applicable.

AML onset, peripheral blast percentage), the CR rate of the DA group remained significantly elevated compared to the referent AA group (OR = 4.06; 95% CI, 1.05-18.6). Similar results were obtained if the 4 haplotypes having fewer than 20 patients were combined into a single category. It was also noted that patients with D haplotypes (DA/DB/DC) had a somewhat higher CR rate (47 of 89, 53%) than those without D (34 of 102, 33%). Complementing the higher CR rate in patients with D haplotypes, these patients also had a lower RD rate (21 of 89, 24%) compared to those without D haplotype (43 of 102, 42%). Similarly, the adjusted estimates resulted in significantly better response to induction chemotherapy (OR = 3.06; 95% CI 1.44-6.70) and lower risk of resistant disease (OR = 0.32; 95% CI, 0.14-0.72). The significant differences in CR and RD rates between the D and non-D haplotype groups were not reflected in OS, although patients with D haplotype had somewhat better OS (HR = 0.80; 95% CI, 0.57-1.14; Table 4).

Analysis of toxicity profiles

Three of the 200 patients were not evaluated for toxicities for the following reasons: refusal to continue participation after 1 day, death on first day of treatment, and institutional failure to submit data. Occurrences of specific toxicities within each organ group are shown in Table 5. For analysis, however, toxicities were grouped into broad categories because many specific toxicities were not frequent enough to warrant separate analyses and because specific toxicities may result from multiple types of tissue damage.

Of the 197 patients evaluated for toxicity of induction chemotherapy, 178 (90%) experienced a total of 532 GI toxicities, 66 patients (34%) had a total of 102 liver toxicities, 61 patients (31%) experienced a total of 90 lung toxicities, 74 metabolic toxicities were reported for 43 patients (23%), and 36 patients (18%) experienced 44 GU toxicities.

Tables 6 and 7 summarize the results of polychotomous logistic regression analysis of the 5 categories of toxicities. As shown in these tables, some toxicity effects were associated with several genotypes or haplotype categories. Carriers of *XRCC3* variant TT genotype had significantly decreased risk of liver toxicity (OR = 0.32; 95% CI, 0.11-0.95). Polymorphisms in *ERCC1* were associated with reduction in risk of metabolic toxicities, with a significant decrease in risk for patients with CA genotypes (OR = 0.41 with 95% CI, 0.19-0.90) and a large but nonsignificant decrease in risk among the 4 patients with AA genotype. Carriers of

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Table 4. Analyses of treatment outcomes by *XPD* haplotypes

		CR			RD			OS		
***XPD* Haplotype**	**Total no.**	**No.**	**OR**	**CI**	**No.**	**OR**	**CI**	**No. of deaths**	**HR**	**CI**
AA*	72	25	1.00	NA	34	1.00	NA	67	1.00	NA
AC	11	3	0.75	0.10-4.85	3	1.20	0.19-6.94	10	1.80	0.78-4.19
BB	13	5	0.48	0.04-3.88	3	0.62	0.06-4.60	*12*	2.82	1.02-7.76
BC	6	1	0.35	0.02-2.79	3	1.14	0.17-7.84	6	2.09	0.88-4.97
DA	22	16	4.06	1.05-18.6	5	0.34	0.06-1.46	20	0.94	0.50-1.76
DB	13	6	3.94	0.82-22.7	3	*0.12*	*0.01-0.87*	12	0.73	0.35-1.55
DC	54	25	2.17	0.89-5.42	13	0.36	0.14-0.92	50	0.96	0.63-1.46
AA*	72	25	1.00	NA	34	1.00	NA	67	1.00	NA
DA	22	16	4.07	1.06-18.5	5	0.35	0.06-1.47	20	0.92	0.49-1.71
DC	54	25	2.16	0.89-5.37	13	0.38	0.14-0.92	50	0.96	0.63-1.47
Other	43	15	1.12	0.39-3.16	12	0.58	0.20-1.62	40	1.32	0.82-2.14
AA/AC/BB/BC*	102	34	1.00	NA	43	1.00	NA	95	1.00	NA
DA/DB/DC	89	47	3.06	1.44-6.70	21	0.32	0.14-0.72	82	0.80	0.57-1.14

Estimates of ORs and HRs are adjusted for the following covariates: age (continuous), AML onset (de novo versus secondary), cytogenetic group (favorable, intermediate, unfavorable, unknown), peripheral blast percentage (continuous, unknown for 7 patients who are excluded from multivariate analyses).

NA indicates not applicable.

*Referent haplotype or haplotype category.

at least one *ERCC1* variant A allele had more than a halving of risk, compared to those with CC genotypes (OR = 0.39; 95% CI, 0.19-0.82; $P = .041$). There was also a borderline decrease in risk of lung toxicity for those with AA genotype (OR = 0.16; 95% CI, 0.02-1.02; $P = .037$), although there was no reduction in risk for heterozygotes. Borderline reduction in risk of lung toxicity was noted for *XPD* Lys751Gln heterozygotes (OR = 0.54; 95% CI, 0.28-1.02). *XPD* Asp312Asn polymorphism was associated with reduced GU toxicity for patients with variant AA genotype (OR = 0.27; 95% CI, 0.09-0.81) and reduced GI toxicity for heterozygotes (OR = 0.54; 95% CI, 0.51-0.95). Analyses of toxicities by haplotypes were limited to those with combined haplotype categories because several of the individual haplotypes had too few patients for analysis. Patients with at least one D haplotype, as compared to all other haplotypes, had a 2-fold increase in risk of liver toxicity (OR = 2.00; 95% CI, 1.08-3.82). Individuals with DC haplotype had a decreased risk of GI toxicity.

Discussion

In this study, we sought to determine if SNPs in DNA repair pathways have an impact on therapeutic outcomes of patients with AML. Only *XPD* Lys751Gln and Asp312Asn polymorphisms were associated with major treatment outcomes: CR to induction chemotherapy, RD, or OS. In particular, there was reduced risk of resistant disease for patients with variant *XPD* Lys751GLn genotypes, *XPD* Asp312Asn heterozygotes, and patients possessing *XPD* Gln751C/Asp312G (‘D’) haplotypes. The latter haplotype was also associated with better CR to treatment. Significantly decreased OS was noted for *XPD* 312Asn variant genotype carriers and Gln751C/Asn312A (‘B’) haplotype. We also noted associations between several genotypes, as well as *XPD* haplotypes, and toxicities experienced.

The SNPs under investigation in this study involve several DNA repair pathways, including BER, DSB, and NER pathways. Since this study was initiated several years ago, the field of genomics has rapidly advanced, and there are accumulating data regarding numerous SNPs and haplotype blocks in most genes, including those under study. However, at the time this study was begun and genes and polymorphisms were selected, we selected SNPs based on those that were known in the literature and focused on genes most likely to play a role in treatment response. The earlier published reports on significance of BER, NER, and homologous recombination repair (HRR) DNA repair pathways in leukemogenesis, as well as significance of *XRCC1* Arg399Gln, *APE1* Asp148Glu, *XRCC3* Thr241Met, and *XPD* Lys751Gln and Asp312Asn SNPs in modifying DNA repair functional capacity and carcinogenesis, influenced the selection of these particular SNPs for this study. *ERCC1* was selected because of its role in NER mechanism of DNA repair.

To the best of our knowledge, except for the *XPD* Lys751Gln polymorphism, this is the first report on relationships between selected gene candidates in DNA repair pathways and therapeutic outcomes of patients with AML, although the genes evaluated in this analysis have been studied in relation to other cancer outcomes. Several studies previously reported associations between *ERCC1* codon 8092 and *ERCC1* codon 118 variant genotypes and poorer survival outcomes in cancer patients diagnosed with non–small-cell lung cancer[23,25,26] and colorectal cancer.[28,29] Data from Stoehlmacher et al[41] indicated that patients with colorectal cancer carrying at least one Gln mutant allele of *XRCC1* Arg399Gln SNP were at a 5.2-fold (95% CI, 1.21-22.07) increased risk to develop resistance to the 5-fluorouracil/oxaliplatin chemotherapy. Yoon et al[42] recently reported that *XRCC1* polymorphisms and haplotypes were significant predictors of progression-free survival in patients with lung cancer. In contrast, Berwick et al[43] noted no associations between SNPs in *XRCC1*-Arg399Gln, *XRCC3*-Thr241Met, and *XPD*-Lys751Gln and survival outcomes in 120 patients with soft tissue sarcoma. In a study of 320 pediatric patients with acute lymphoblastic leukemia, Krajinovic et al[44] reported no significant associations between polymorphic *APE1* 148Glu and *XRCC1* 194Trp variants and event-free survival. There have been recent studies of *XPD*, involved in NER, and survival of patients with AML.[18] In a study of 341 elderly patients with AML conducted by researchers in the United Kingdom, modestly increased HRs of 1.30 and 1.18 were found for disease-free and overall survival, respectively, by *XPD* variant genotypes. However, in a study of pediatric AML conducted by the Children’s Oncology Group (COG),[45] survival and treatment-related mortality were not associated with *XPD* codon 751 genotypes.

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Table 5. Occurrence of selected toxicities in 197 patients

Toxicities evaluated	No. of patients	%
GU toxicity		
Creatinine increase	27	14
Renal failure	5	3
Incontinence	4	2
Urinary retention	3	2
Proteinuria	2	1
Vaginitis	2	1
GU other	1	1
GI toxicity		
Nausea	117	59
Diarrhea	107	54
Stomatitis/pharyngitis	79	40
Anorexia	78	40
Vomiting	69	35
Constipation/bowel obstruction	36	18
Gastritis/ulcer	14	7
Esophagitis/dysphagia	8	4
Dyspepsia/heartburn	4	2
Taste disturbance	4	2
GI mucositis, NOS	3	2
Ileus	3	2
Salivary changes, NOS	2	1
Colitis	1	1
Dehydration	1	1
Mouth dryness	1	1
GI other	5	3
Liver toxicity		
Bilirubin increase	49	25
Alkaline phosphatase or 5′—nucleotidase increase	27	14
Transaminase increase	24	12
Liver, clinical	1	1
Liver, other	1	1
Lung toxicity		
Dyspnea	35	18
Cough	22	11
Pulmonary edema	16	8
Pneumonitis/infiltrates	10	5
ARDS	2	1
Hiccoughs	1	1
Lung, other	4	2
Metabolic toxicity		
Hypokalemia	25	13
Hypocalcemia	20	10
Hyperglycemia	11	6
Hyponatremia	10	5
Hypomagnesemia	4	2
Hypoglycemia	1	1
Hypophosphatemia	1	1
Hypothyroidism	1	1
Metabolic, other	1	1

Toxicities were classified according to SWOG criteria for SWOG—9031 and to National Cancer Institute Common Toxicity Criteria version 2.0 for SWOG—9333.

ARDS indicates acute respiratory distress syndrome.

The literature on associations between germline polymorphic DNA repair variants and treatment outcomes of cancer patients is conflicting and indicates that effects of DNA repair gene polymorphisms, if found, are usually small. Associations may largely depend on such important factors as type of cancer, its stage, functional DNA repair capability of polymorphic variants, and interactions of polymorphic enzymes with therapeutic agents. Clearly, these analyses need to be conducted in larger populations. It is also worth mentioning that multiple genes in several DNA repair pathways more than likely interact with each other during repair processes.[46,47] Therefore, altered enzyme activities determined by DNA repair polymorphic genes could be compensated for by enhanced/reduced activity of their counterparts.

The noted associations between reduced risk of development of RD and *XPD* variant genotypes in this study is consistent with the hypothesis that insufficient DNA repair activity, encoded by variations in DNA repair genes, facilitates tumor-cell apoptosis, and reduces repair of genetically damaged cells. Better therapeutic outcomes associated with ‘D’ haplotypes in our study were consistent for both CR and RD. Haplotyping for these variants in larger studies, with other AML populations, would certainly be beneficial to confirm these findings and in the search for novel prognostic determinants and molecular targets of this lethal, in most cases, malignancy. Null results for OS in our study, except for the significant findings of decreased OS for *XPD* 312 Asn/Asn variant genotype and Gln751C/Asn312A (‘B’) haplotype, may be due to the poor survival rates of elderly patients with AML, due to both the disease and to the treatment. The aggressive induction chemotherapy regimens and deaths due to treatment complications, as well as rapid disease progression, may overwhelm the subtle effects of variations in DNA repair on treatment outcomes. Furthermore, the dose of daunorubicin used in these trials of elderly patients was not high, and the poor CR rates could also be due, in part, to inadequacy of treatment given, thus masking potential effects of DNA repair variability.

The relationships between treatment received, toxicities experienced, and potential dose reduction due to toxicities could have an effect on therapeutic outcomes. However, in these trials, only 9 of the 197 patients were removed from protocol remission induction therapy due to toxicity, side effects, or complications of treatment, and for only one of these 9 was liver toxicity identified as a possible reason for removal from protocol therapy (the other reasons were most often infection or hemorrhage/thrombocytopenia). Although it is possible that treatment dose reductions were made in response to liver toxicities in some patients, our database does not contain this information.

Inherited variations in DNA repair enzymes likely not only affect apoptosis of tumor cells but also susceptibility of normal cells to incur damage. In fact, dose adjustments of chemotherapeutic agents in cases of severe treatment-related toxicity have been made possible by the identification of functional polymorphisms in enzymes encoded by drug metabolizing genes, as is the case for genotyping for thiopurine S-methyltransferase (TPMT) polymorphisms among children treated with thiopurines for acute lymphoblastic leukemia.[48] However, few studies have investigated the role of DNA repair gene polymorphisms and toxicity outcomes. In a study by Suk et al[34] of non–small-cell lung cancer, the *ERCC1* C8092A allele was associated with more than a 2-fold increase in risk of grade 3 to 4 GI toxicities in response to platinum chemotherapy. In relation to breast cancer, we (C.B.A.) evaluated relationships between 6 DNA repair gene polymorphisms,[35] including *XRCC1* Arg399Gln and *APE1* Asp148Glu, and development of acute skin toxicity in response to radiotherapy among 446 breast cancer patients. Decreased risk of radiotoxicity was observed for normal-weight women with *APE1* 148Glu and *XRCC1* 399Gln alleles separately, with greatest risk reduction among carriers of both variant alleles in 2 genes (HR = 0.19; 95% CI, 0.06-0.56). However, an earlier report by Moullan et al[49] noted opposite effects of *XRCC1* genotypes on radiotoxicity. Due to the lack of data on functional properties of many SNPs in DNA repair genes, and the

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Table 6. Results of logistic regression analysis on DNA repair genotypes and selected toxicity categories

Gene	No.	Patients		Liver toxicity		Lung toxicity		Metabolic toxicity		GU toxicity		GI toxicity	
		No.	%	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
APEX1	178	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GG		52	29.21	1	NA	1	NA	1	NA	1	NA	1	NA
GT		73	41.01	1.5	0.70-3.18	1.48	.69-3.19	1.31	0.51-3.37	1.06	0.41-2.74	0.99	0.52-1.90
TT		53	29.78	1.24	0.56-2.75	1.39	0.61-3.24	0.61	0.24-1.52	0.71	0.27-1.84	0.59	0.29-1.20
GT or TT		126	70.79	1.38	0.70-2.67	1.45	0.71-2.87	0.92	0.39-2.02	0.88	0.38-2.05	0.8	0.44-1.46
XRCC1	194	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GG		91	46.91	1	NA	1	NA	1	NA	1	NA	1	NA
GA		87	44.85	0.7	0.37-1.31	1	0.53-1.91	1.24	0.59-2.66	0.8	0.35-1.80	0.68	0.39-1.17
AA		16	8.25	1.2	0.39-4.56	0.96	0.33-3.21	1.94	0.49-12.98	0.78	0.22-3.70	1.27	0.46-3.50
GA or AA		103	53.09	0.76	0.41-1.39	0.99	0.54-1.83	1.32	0.64-2.75	0.8	0.36-1.72	0.74	0.44-1.25
XRCC3	185	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CC		94	50.81	1	NA	1	NA	1	NA	1	NA	1	NA
CT		75	40.54	0.95	0.50-1.83	1.65	0.86-3.24	1.18	0.56-2.57	0.97	0.44-2.19	0.98	0.56-1.71
TT		16	8.65	0.32	0.11-0.95	2.53	0.76-11.51	1.84	0.46-12.30	0.79	0.22-3.74	0.53	0.21-1.33
CT or TT		91	49.19	0.79	0.43-1.45	1.77	0.95-3.36	1.27	0.61-2.65	0.93	0.44-2.01	0.87	0.51-147
ERCC1	199	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CC		149	74.87	1	NA	1	NA	1	NA	1	NA	1	NA
CA		46	23.12	0.69	0.35-1.41	1.82	0.84-4.27	0.41	0.19-0.90	0.75	0.33-1.84	1.12	0.61-2.05
AA		4	2.01	1.33	0.18-26.60	0.16	0.02-1.02	0.23	0.04-1.81	Inf (n=4)*	0.31−∞*	0.58	0.08-4.18
CA or AA		50	25.13	0.73	0.37-1.46	1.37	0.68-2.95	0.39	0.19-0.82	0.84	0.37-2.04	1.07	0.59-1.93
***XPD* Lys751Gln**	194	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
AA		84	43.30	1	NA	1	NA	1	NA	1	NA	1	NA
AC		83	42.78	1.59	0.83-3.11	0.54	0.28-1.02	1.57	0.73-3.48	0.88	0.37-2.06	0.66	0.38-1.16
CC		27	13.92	1.06	0.44-2.68	1.40	0.50-4.54	0.95	0.37-2.68	0.38	0.14-1.09	1.36	0.62-3.01
AC or CC		110	56.70	1.42	0.78-2.61	0.65	0.35-1.20	1.35	0.68-2.72	0.69	0.31-1.47	0.80	0.47-1.34
***XPD* Asp312Asn**	190	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GG		95	50.00	1	NA	1	NA	1	NA	1	NA	1	NA
GA		76	40.00	1.25	0.65-2.45	0.76	0.40-1.44	1.28	0.60-2.81	0.79	0.34-1.87	0.54	0.31-0.95
AA		19	10.00	0.44	0.17-1.18	0.78	0.28-2.39	0.79	0.27-2.64	0.27	0.09-0.81	1.07	0.42-2.73
GA or AA		95	50.00	0.99	0.54-1.82	0.76	0.41-1.39	1.14	0.57-2.32	0.60	0.27-1.28	0.62	0.36-1.04

NA indicates not applicable.

*No GU toxicities among patients with *ERCC1* AA genotype resulted in infinite OR estimates.

limited epidemiologic reports on their associations with toxicity outcomes in cancer patients, our results on associations between reduced toxicities and *ERCC1*, *XPD*, and *XRCC3* polymorphisms must be interpreted with caution.

One of the selected polymorphisms for this study at the IVS5 + 34C > A region of *ERCC1* gene occurs in an intron. It is of interest that the cluster of DNA repair genes, including *ERCC1*, is mapped to chromosome region 19q13.2-13.3. Although biologic functions of introns are largely unknown, in a study of basal-cell carcinoma, a significant association with risk was found for the RAI intronic allele A, located in the IVS5 + 34C > A region in close proximity to the *XPD* gene on chromosome 19.[50] Pharmacogenetic associations found for the *ERCC1* polymorphisms in this study might also be explained by potential gene-gene interactions, as well as linkage disequilibrium between the gene markers.

This study benefits from having been conducted in the context of cooperative group clinical trials, with a fairly homogeneous population of patients who were treated with the same drug regimen. This is often not the case for retrospective pharmacogenetic studies and strengthens the likelihood that findings are not due to artifactual confounding of treatment and genotype. Because of the nature of the clinical trials, toxicities experienced were carefully monitored and recorded, and we were able to evaluate potential associations between DNA repair genotypes and haplotypes and several types of toxicities associated with treatment.

The use of data and specimens from cooperative group trials for pharmacogenetic studies also introduces some potential limitations. The 200 patients recruited for this study were from 66 different centers, and it is possible that there could be differences in

Table 7. Results of logistic regression analysis on *XPD* haplotypes and selected toxicity categories

XPD haplotype	Patients		Liver toxicity		Lung toxicity		Metabolic toxicity		GU toxicity		GI Toxicity	
	No.	%	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
AA*	72	37.70	1	NA	1	NA	1	NA	1	NA	1	NA
DA	22	11.52	2.44	0.82-9.07	0.94	0.34-2.88	3.60	0.93-23.8	1.00	0.27-4.77	1.04	0.42-2.57
DC	54	28.27	1.60	0.75-3.55	0.55	0.26-1.16	1.56	0.66-3.94	0.84	0.31-2.37	*0.45*	*0.23-0.85*
Other	43	22.51	0.93	0.43-2.05	0.98	0.42-2.35	1.28	0.53-3.25	0.42	0.16-1.09	0.99	0.48-2.04
AA/AC/BB/BC*	102	46.60	1	NA	1	NA	1	NA	1	NA	1	NA
DA/DB/DC	89	53.40	2.00	1.08-3.82	0.72	0.39-1.33	1.69	0.83-3.56	1.33	0.62-2.92	0.66	0.39-1.12

NA indicates not applicable.

*Referent haplotype or haplotype category.

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outcomes between sites. However, most centers put few patients on the studies; specifically, 51 centers had fewer than 5 patients each in this data set, with 21 centers having only one patient. Only one center had more than 10 patients. Because most centers had so few patients, it is not possible to determine conclusively whether or not outcomes differed between centers, especially because this would require adjustment for other established prognostic factors such as age, AML onset (de novo versus secondary), cytogenetics, performance status, and so on.

There was also some heterogeneity in supportive care between the 2 studies, because the studies were conducted over different time periods (SWOG-9031, November 1991 to February 1994; SWOG-9333, February 1995 to December 1998) and recommendations for care during treatment did evolve with time. For example, SWOG-9333 recommended, but did not require, the use of prophylactic antibiotics during induction, whereas SWOG-9031 did not. The 2 protocols also differed slightly in blood product support plans and had different recommendations for infection management, although neither protocol had required infection management plans. However, even if these potential differences in supportive care resulted in differences in toxicities experienced or survival outcomes, there is no reason to believe that there would be systematic differences in genotypes and haplotypes by study; thus, associations between genotypes/haplotypes and treatment outcomes are unlikely to be affected by study enrollment.

The patients included in this analysis were those who had sufficient WBCs available in the tissue bank, and these patients had significantly higher WBC counts than those from the same studies who were not included. However, there were no significant differences in treatment outcomes between those included and excluded in the molecular analysis, with the estimated HR (excluded relative to included) for mortality 1.07 (95% CI, 0.87-1.31; $P = .54$). Nonetheless, results from these analyses may not be representative of the larger patient population.

Due to numerous comparisons in analyses, and fairly small number of patients with particular genotypes and haplotypes and specific toxicities developed, there is certainly a possibility that our findings were due to chance. However, these results may also indicate that variations in the pathways for NER and possibly DSB repair could be of more importance in AML pathogenesis than other DNA repair mechanisms. Although the findings of associations between specific toxicities and genotypes and haplotypes clearly need to be replicated in additional patient populations, they introduce a potential for practical pharmaceutical applications in individualized dose adjustments and drug selection for optimized chemotherapy. Because of the lack of definitive data on the functional significance of many SNPs and haplotypes in DNA repair pathways, future studies should also assess their role in modifying treatment-related toxicities and OS.

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Authorship

Contribution: N.K. participated in analysis and interpretation of data and was a primary author of manuscript; K.J.K. designed parent trials, assisted in design of pharmacogenetics study and analysis of data, and contributed to manuscript writing; J.G. participated in design and conduct of parent trials, assisted in design and coordination of pharmacogenetic study, and contributed to manuscript writing; J.A. participated in design and conduct of parent trials and contributed to manuscript writing; A.H. participated in design and implementation of pharmacogenetic study and contributed to manuscript writing; C.L.W. participated in design and conduct of parent trials, design and coordination of pharmacogenetic study, and contributions to manuscript writing; M.L.S. participated in design and conduct of parent trials; contributed to manuscript writing; C.B.A. designed the pharmacogenetic study from conception to implementation, coordinated genotyping, participated in data analysis, and was the senior contributor to the manuscript.

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