# Polymorphisms in *ERCC1* and Grade 3 or 4 Toxicity in Non–Small Cell Lung Cancer Patients

**Rebecca Suk, Sarada Gurubhagavatula, Sohee Park, Wei Zhou, Li Su, Thomas J. Lynch, John C. Wain, Donna Neuberg, Geoffrey Liu, and David C. Christiani**

Massachusetts General Hospital and Harvard School of Public Health, Boston, Massachusetts

## ABSTRACT

***Purpose:*** **ERCC1 is a lead enzyme in the nucleotide excision repair pathway of DNA repair. Polymorphisms have been identified in the *ERCC1* gene, the *C8092A* and codon 118 polymorphisms, which may lead to an altered capacity to regenerate damaged normal tissue and greater treatment-related toxicity.**

***Experimental Design:*** **Using logistic regression models, we evaluated the *ERCC1 C8092A* and codon 118 polymorphisms and their association with the occurrence of grade 3 or 4 toxicity in 214 stage III and IV non–small cell lung cancer patients treated first line with platinum-based chemotherapy. Adjusting covariates were performance status and type of treatment regimen.**

***Results:*** **There was no statistically significant association between either the *C8092A* or codon 118 polymorphism and overall or hematologic grade 3 or 4 toxicity. However, carrying at least one variant *ERCC1 C8092A* allele was associated with a significantly increased risk of grade 3 or 4 gastrointestinal toxicity (adjusted odds ratio, 2.33; 95% confidence interval, 1.07-5.05; $P = 0.03$).**

***Conclusions:*** **Adjusting for performance status and type of treatment regimen, carrying at least one *ERCC1 8092A* allele is associated with a >2-fold increase in grade 3 or 4 gastrointestinal toxicity among platinum-treated non–small cell lung cancer patients.**

## INTRODUCTION

Lung cancer is the leading cause of cancer mortality among both men and women in the United States, with over 170,000 new cases and over 150,000 deaths estimated in 2003. Non–small cell lung cancer (NSCLC) accounts for over 80% of all lung cancer cases. Most patients with NSCLC are diagnosed in the advanced stages, with the majority of patients presenting with stage III or IV disease. Survival for patients in these late stages of disease remains poor, with 5-year survival rates in stage IIIA of 13%, stage IIIB of 3% to 7%, and stage IV of 1% (1).

Chemotherapy can prolong survival for NSCLC. Platinum-based doublets are the standard of care for stage IV disease, whereas the combination of chemotherapy with radiation has been shown to have benefit in the treatment of stage III NSCLC (2). However, treatment-related toxicity remains a major consideration in treatment planning, as severe toxicities can hamper the quality of life of patients.

It is not currently known how to predict which patients will have severe dose-limiting toxicities with the treatment regimens most commonly used for NSCLC. Genetic polymorphisms in pathways of drug activity and metabolism may be associated with differential effects on toxicity. For example, irinotecan is metabolized from the active form SN38 to the inactive SN38G by the hepatic enzyme UDP glucuronosyltransferase-1A1 (UGT1A1). Investigators have shown that polymorphisms in *UGT1A1* are associated with more severe grades of neutropenia (3). Identifying candidate genes and elucidating which polymorphisms are associated with dose-limiting toxicity may allow clinicians to make more rational treatment choices in the future.

In lung cancer, genetic polymorphisms have been studied in relation to the risk of cancer (4–6) and survival outcome (7, 8) but not in relation to toxicity. Particular interest has focused on genes involved in DNA repair, including the base excision repair, nucleotide excision repair, mismatch repair, and double-strand break repair pathways. It is hypothesized that deficiencies in DNA repair will increase the risk of acquiring cancers, as individuals carrying such polymorphisms are less proficient in repairing carcinogen-induced damage. Conversely, deficient DNA repair may be associated with increased response to therapies which act by disrupting DNA replication to kill cancer cells. However, deficient DNA repair may also predict for increased toxicity, due to decreased capacity to repair normal bystander cells damaged by treatment.

The platinum agents, which are a component of most first-line regimens in NSCLC, act by forming bulky adducts to DNA which interfere with replication. Nucleotide excision repair (NER) is one of the key pathways by which cells repair platinum-induced DNA damage. A series of proteins act to recognize base damage, unwind DNA, remove the damaged single-stranded fragment, and synthesize a correct strand in its place (9). ERCC1 is a key enzyme in the NER pathway. The ERCC1-XPF heterodimer acts as an endonuclease that incises 5′ to the damaged DNA strand, allowing removal of the damaged strand and polymerization and religation (10–12). Polymorphisms in *ERCC1* have been shown to be associated with increased risk of squamous cell carcinomas of the head and neck (13) and oligoastrocytomas (14), although the association with lung cancer is less clear (15). High levels of intratumoral ERCC1 mRNA have been associated with platinum

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**Requests for reprints:** David Christiani, Harvard School of Public Health, I-1407, 665 Huntington Avenue, Boston, MA 02115. Phone: 617-432-3323; Fax: 617-432-3441; E-mail: dchristi@hsph.harvard.edu.

*Table 1* Patient characteristics

| Patient characteristic | | *n* (%) |
|---|---|---|
| Total no. of patients | | 214 |
| Median age (range) | 61 (33-84) | |
| Male | | 108 (51) |
| Female | | 106 (49) |
| PS | | |
| PS = 0, 1 | | 201 (94) |
| PS ≥2 | | 13 (6) |
| Stage | | |
| Inoperable early stage* | | 8 (4) |
| Stage IIIA | | 69 (32) |
| Stage IIIB | | 64 (30) |
| Stage IV | | 73 (34) |
| Treatment type | | |
| No radiation | | 67 (31) |
| Radiation + carboplatin | | 86 (40) |
| Radiation + cisplatin | | 61 (29) |
| Histological cell type | | |
| Adenocarcinoma | | 113 (53) |
| Large cell | | 43 (20) |
| Squamous cell | | 28 (13) |
| Other | | 30 (14) |
| *ERCC1 8092* | | |
| *C/C* | | 118 (55) |
| *C/A* | | 82 (38) |
| *A/A* | | 14 (7) |
| *ERCC1* codon 118 | | |
| *T/T* | | 79 (37) |
| *T/C* | | 99 (46) |
| *C/C* | | 36 (17) |

Abbreviation: PS, polymorphism status.
*Due to comorbidities.

resistance in the treatment of ovarian (16, 17), cervical (18), gastric (19), colon (20, 21), and lung cancers (22). However, the role of *ERCC1* in toxicity outcomes has not been explored. In this study, we investigate the association of two previously identified polymorphisms in *ERCC1*, the codon 118 polymorphism (23) and the *C8092A* polymorphism (24), with grade 3 or 4 toxicity in patients treated with platinum for NSCLC.

## METHODS

**Study Population.** The study subjects were drawn from an ongoing molecular epidemiologic study, which has been described previously (25). In brief, newly diagnosed lung cancer cases and their spouse or friend controls have been enrolled since 1992 as part of a study to evaluate genetic polymorphisms and risk and outcomes in lung cancer. From 1992 to 1996, patients were recruited from the thoracic surgery wards at Massachusetts General Hospital (MGH); most of these surgical patients had early-stage lung cancer and did not receive chemotherapy. From 1997 onwards, cases were recruited from all patients presenting to the thoracic oncology, thoracic surgery, and pulmonary services at MGH; both early-stage and advanced-stage patients have been enrolled during these years. Thus, the majority of our NSCLC patients were derived from 1997 onwards, because most patients receiving chemotherapy had advanced-stage disease.

Eligible cases for the present study included all histologically diagnosed NSCLC cases with advanced-stage disease who received first-line platinum chemotherapy at MGH. The study was approved by the Institutional Review Boards at MGH and the Harvard School of Public Health.

**Data Collection.** The incidence of grade 3 or 4 toxicity during first-line chemotherapy, as defined by the National Cancer Institute Common Toxicity Criteria version 3.0, was collected by an investigator who was blinded to the polymorphism status of the patients. Toxicities included neutropenia, anemia, thrombocytopenia, febrile neutropenia, nausea, vomiting, esophagitis, diarrhea, and neuropathy. Patient charts were reviewed to extract data on toxicities experienced during chemotherapy. The complete medical record, including progress notes of the treating oncologist and treating nurses, laboratory data, and chemotherapy infusion orders and infusion flowsheets, was reviewed to collect these data. Since 1998, chemotherapy orders have been computerized, and treatment alterations such as dose adjustments or treatment delays have prompted a request for a rationale from the ordering physician. A computerized longitudinal medical record simplified the process of collecting toxicity data, as physicians, chemoinfusion nurses, and ancillary staff use standardized templates for notes, orders, and procedures. In addition, a system to standardize toxicity grade has been in place for all patients, given that a proportion of them were in clinical trials. Each of these conditions improved the ability to assess toxicity uniformly across patients.

***ERCC1* Genotyping.** Blood samples were collected from all study subjects at the time of recruitment. DNA was extracted from peripheral blood samples using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN). The *ERCC1 C8092A* and codon 118 polymorphisms were genotyped by the 5-nuclease assay (Taqman) using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). The primers, probes, and reaction conditions were available upon request. Genotyping was done by laboratory personnel blinded to case status, and a random 5% of the samples were repeated to validate genotyping procedures. Two authors independently reviewed the genotyping results, data entry, and statistical analyses.

**Statistical Analysis.** Toxicity outcomes were grouped into (a) any grade 3 or 4 toxicity, (b) any grade 3 or 4 hematologic toxicity, and (c) any grade 3 or 4 gastrointestinal toxicity. Toxicity outcome in each of these groups was dichotomized by the presence or absence of grade 3 or 4 toxicity during first-line treatment. Logistic regression models were used to assess the association between toxicity outcomes and each *ERCC1* polymorphism. Adjusting covariates were performance status and type of treatment regimen (no radiation, radiation and cisplatin, radiation and carboplatin). Reported *P*s were two sided and a level of 0.05 was considered statistically significant. All statistical analyses used SAS version 8.2 (Cary, NC).

## RESULTS

**Patient Characteristics.** Table 1 describes the demographic, histologic, treatment profiles, and *ERCC1* polymorphism status of the study subjects. There were 214 patients treated with platinum chemotherapy as first line at MGH who had medical records available. The median age was 61 years with a range from 33 to 84. Fifty-one percent were male. Eight (4%)

had inoperable early-stage disease, 69 (32%) had stage IIIA, 64 (30%) had stage IIIB, and 73 (34%) had stage IV disease. Adenocarcinoma was the most common histology ($n$ = 113, 53%), with large cell ($n$ = 43, 20%) and squamous cell carcinoma ($n$ = 28, 13%) being less common. The majority (94%) of patients had an Eastern Cooperative Oncology Group performance status of 1 or better. All patients received a platinum agent. Sixty-seven (31%) received platinum without radiation, 86 (40%) received radiation and carboplatin, and 61 (29%) received radiation and cisplatin. For the *ERCC1 C8092A* polymorphism, 118 (55%) patients were homozygous for the wild-type allele (*C/C*), whereas 82 (38%) were heterozygous (*C/A*) and 14 (7%) were homozygous variant (*A/A*). For the codon 118 polymorphism, 79 (37%) patients had the reference *T/T* genotype, whereas 99 (46%) were *T/C*, and 36 (17%) were *C/C*. The two polymorphisms were linked.

**Toxicity Outcomes.** Table 2 shows the toxicity outcomes in our patient population. One hundred and twenty-one (57%) patients experienced grade 3 or 4 toxicity of any kind during the course of platinum-based chemotherapy. Eighty-nine (42%) patients experienced grade 3 or 4 hematologic toxicity. Seventy-nine (37%) had grade 3 or 4 neutropenia, 19 (9%) had grade 3 or 4 febrile neutropenia, 10 (5%) had grade 3 or 4 anemia, and 12 (6%) had grade 3 or 4 thrombocytopenia. Some patients experienced more than one of the toxicities. Thirty-four (16%) patients experienced grade 3 or 4 gastrointestinal toxicity. Twenty (9%) had grade 3 or 4 esophagitis, 11 (5%) had grade 3 or 4 nausea, and five (2%) had grade 3 or 4 vomiting.

***ERCC1* and Toxicity Outcomes.** The *ERCC1 C8092A* polymorphism was not statistically significantly associated with increased risk of overall grade 3 or 4 toxicity [adjusted odds ratio (AOR), 1.48; 95% confidence interval (95% CI), 0.83-2.62; $P$ = 0.18; Table 3]. Analysis of grade 3 or 4 hematologic toxicity again revealed no statistically significant association (AOR, 1.06; 95% CI, 0.59-1.91; $P$ = 0.84; Table 3). However, the incidence of grade 3 or 4 gastrointestinal toxicity was significantly higher in those patients carrying at least one variant allele (AOR, 2.33; 95% CI, 1.07-5.05; $P$ = 0.03; Table 3).

We also analyzed the codon 118 polymorphism for association with toxicity. There was no significant association between the codon 118 polymorphism and risk of overall toxicity (AOR, 1.20; 95% CI, 0.67-2.15; $P$ = 0.54; Table 4), hematologic toxicity (AOR, 1.08; 95% CI, 0.59-1.98; $P$ = 0.80; Table 4), or gastrointestinal toxicity (AOR, 1.47; 95% CI, 0.66-3.28; $P$ = 0.34; Table 4).

*Table 2* Toxicity outcomes

| | *n* (%) |
|---|---|
| Total no. of patients | 214 |
| Any grade 3 or 4 toxicity | 121 (57) |
| Any grade 3 or 4 hematologic toxicity | 89 (42) |
| Neutropenia | 79 (37) |
| Febrile neutropenia | 19 (9) |
| Anemia | 10 (5) |
| Thrombocytopenia | 12 (6) |
| Any grade 3 or 4 gastrointestinal toxicity | 34 (16) |
| Esophagitis | 20 (9) |
| Nausea | 11 (5) |
| Vomiting | 5 (2) |

*Table 3* AORs of grade 3 or 4 toxicity with *ERCC1 C8092A* polymorphism

| *ERCC1 C8092A* | Total, *n* | Grade 3 or 4 toxicity | *n* (%) | AOR (95% CI) | *P* |
|---|---|---|---|---|---|
| *C/C* | 118 | Gastrointestinal | 14 (12) | 1.00 (reference) | 0.03 |
| *C/A, A/A* | 96 | | 20 (21) | 2.33 (1.07-5.05) | |
| | | Hematologic | 48 (41) | 1.00 (reference) | 0.84 |
| | | | 41 (43) | 1.06 (0.59-1.91) | |
| | | Overall | 62 (53) | 1.00 (reference) | 0.18 |
| | | | 59 (61) | 1.48 (0.83-2.62) | |

NOTE. AORs are obtained from logistic regression models adjusting for performance status and type of treatment regimen (reference group: no RT, RT + cisplatin, RT + carboplatin).

## DISCUSSION

In this study, we investigated whether polymorphisms in the DNA repair gene *ERCC1* are associated with increased toxicity among patients treated for advanced NSCLC. In the analysis, we adjusted for potential confounding factors of performance status and type of treatment. We grouped treatment type into (a) no radiation, (b) radiation and cisplatin, and (c) radiation and carboplatin, because we thought that these treatment differences were likely to confound toxicity outcomes. We report that carrying at least one *ERCC1 8092A* allele is associated with a significantly increased risk of grade 3 or 4 gastrointestinal toxicity among patients with advanced NSCLC who are treated with platinum chemotherapy, adjusting for performance status and type of treatment regimen. There was no association with the codon 118 polymorphism.

It is interesting that the association was found only with the *C8092A* and not the codon 118 polymorphism. This may reflect inadequate sample size in our study to detect a true difference, or differences inherent in the polymorphisms themselves. The polymorphism at codon 118 is a $C- \geq T$ base change that results in coding for the same amino acid, asparagine. The *C8092A* polymorphism, a $C- \geq A$ change in the 3′ untranslated region, has been suggested to affect mRNA stability (6, 14). Whereas the exact functional consequence of this polymorphism has yet to be elucidated, it is possible that the $C- \geq A$ change leads to destabilization of ERCC1 mRNA and lower expression levels of the enzyme. Lower DNA repair capacity may lead to decreased ability to repair the damage done by platinum agents to normal tissue, and hence increased toxicity. Having sufficient NER activity may be crucial to repairing damage to normal host tissues during the course of cytotoxic treatment and preventing overwhelming treatment-related toxicity.

DNA repair capacity may play paradoxical roles in carcinogenesis, response to cancer treatment, and toxicity. Lower DNA repair capacity as measured by the host cell reactivation assay has been associated with increased risk of developing lung cancer (26, 27), although a specific association with ERCC1 has yet to be found (15). Reduced DNA repair capacity, however, may lead to increased response to therapies that act by damaging the DNA of cancer cells. Indeed, in studies measuring ERCC1 mRNA expression among various tumor cell lines, high levels of expression have been associated with increased resistance to platinum-based chemotherapy (17, 19, 21, 22, 28, 29).

*Table 4* AORs of grade 3 or 4 toxicity with *ERCC1* codon 118 polymorphism

| *ERCC1* | Total, *n* | Grade 3 or 4 toxicity | *n* (%) | AOR (95% CI) | *P* |
|---|---|---|---|---|---|
| *T/T* | 79 | Gastrointestinal | 11 (14) | 1.00 (reference) | 0.35 |
| *T/C, C/C* | 135 | | 23 (17) | 1.47 (0.66-3.28) | |
| | | Hematologic | 31 (39) | 1.00 (reference) | 0.80 |
| | | | 58 (43) | 1.08 (0.59-1.98) | |
| | | Overall | 42 (53) | 1.00 (reference) | 0.54 |
| | | | 79 (59) | 1.20 (0.67-2.15) | |

NOTE. AORs are obtained from logistic regression models adjusting for performance status and type of treatment regimen (reference group: no RT, RT + cisplatin, RT + carboplatin).

Whereas many studies have focused on intratumoral ERCC1 mRNA expression as a predictor of outcome, few have investigated germ line polymorphisms in *ERCC1*. In a retrospective study of metastatic colorectal cancer patients treated with oxaliplatin/5-fluorouracil, a trend toward increased survival with the variant *A* allele of the *ERCC1 C8092A* polymorphism was noted (6).

There have been no studies investigating the role of DNA repair capacity and toxicity outcomes. In our study, we investigated germline polymorphisms in *ERCC1*, which would be expected to affect all tissues in the body. Our finding, that carrying the variant *A* allele of the *C8092A* polymorphism is associated with severe gastrointestinal toxicity, may be due to decreased mRNA stability and decreased NER activity in susceptible tissues, leading to more severe toxicity. The deficient NER activity would render tissue more susceptible to platinum-induced damage.

Our result was specific to gastrointestinal toxicity. Esophagitis reflects a direct damage on the mucosal tissues of the gastrointestinal tract. Chemotherapy-induced nausea/vomiting is thought to be mediated by a complex interplay between the gastrointestinal tract and the central and peripheral nervous systems. Whereas the exact mechanism has yet to be determined, tissue damage to the normal gastrointestinal tissue is thought to be a contributing factor (30). In a post hoc analysis, we excluded patients who experienced nausea or vomiting in the first two weeks of treatment, as early-onset symptoms would more likely reflect primarily central nervous system-mediated toxicity without a significant contribution from gastrointestinal tract tissue damage. In this post hoc subgroup analysis, we found a similar trend towards increased gastrointestinal toxicity with the *ERCC1 C8092A* polymorphism (AOR, 2.01; 95% CI, 0.87-4.64; $P = 0.10$).

We did not find an association between either the *ERCC1 C8092A* or codon 118 polymorphism and hematologic toxicity. The lack of such an association in this study may reflect a true finding, or inadequate sample size, or differential mediation of myelosuppression by treatment which is not fully understood.

Many unanswered questions remain, which will need to be elucidated in further studies: What is the mechanism by which the *C8092A* polymorphism affects mRNA stability? Does the germ line *C8092A* polymorphism correlate with actual ERCC1 mRNA levels in the tissues of interest (for toxicity, the target tissues damaged)? Is there a way to selectively suppress DNA repair capacity in tumor cells whereas enhancing it in the bystander tissues that experience collateral damage and toxicity?

Strengths of this study include the enrollment of a large number of patients without knowledge of polymorphism status and the independent collection of clinical outcomes data and genotyping. Major limitations of this study include its retrospective nature and the possibility for ascertainment bias, particularly with regard to toxicity outcomes. Whereas multiple sources of documentation were searched to capture as much toxicity information as possible, documentation of toxicity is at the discretion of the treating clinicians, and this can vary by physician, by type of regimen being used, and by treatment on or off protocol. Grading of toxicity can also be subjective, although the widespread acceptance and use of the National Cancer Institute Common Toxicity Criteria within the MGH thoracic oncology group has in large part standardized toxicity grading among clinicians. Of note, although there may have been variable recording and grading of toxicity outcomes, it is very unlikely that there would have been a systematic difference based on polymorphism status, which was unknown to the physicians at the time of treatment. Prospective studies will be needed in order eliminate many of these potential biases and to validate the hypotheses generated from this study.

Treatment-related toxicity is an important consideration in the care of patients with advanced NSCLC. We report an increased risk of severe grade 3 or 4 gastrointestinal toxicity among NSCLC patients treated with platinum chemotherapy who carry the variant *A* allele of the *ERCC1 C8092A* polymorphism. This result will need to be validated in prospective trials. As we learn more about how genetic polymorphisms in various genes affect the outcomes of treatment for lung cancer, it may be possible to individualize treatment regimens. It may be possible in the future to select chemotherapies and treatments based on individual genetic profiles, taking into account not only their likelihood of response but also their likelihood of having severe treatment-related toxicities.

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