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The influence of platinum pathway polymorphisms on the outcome in patients with malignant mesothelioma

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Background: Platinum-based therapy is widely used in the treatment of malignant mesothelioma (MM); however, the efficacy and toxicity of platinum agents vary greatly between patients. The aim of our study was to evaluate the influence of platinum pathway polymorphisms on treatment outcome in patients with MM.

Patients and methods: In total, 133 patients with MM treated with (n = 97) or without (n = 36) platinum-based therapy were genotyped for common XPD, ERCC1, and GSTP1 polymorphisms, as well as for GSTM1 and GSTT1 gene deletion. Haplotype analysis was carried out to assess the combined effect of nucleotide excision repair (NER) polymorphisms.

Results: GST polymorphisms were not associated with treatment outcome in patients with MM. In the group of platinum-treated patients with MM, ERCC1 8092C/C wild-type genotype significantly influenced progression-free survival (PFS) in multivariable analysis accounting for clinical variables (P = 0.034). XPD 312Asp/Asp and ERCC1 8092C/C wild-type genotypes also increased the odds of treatment-related toxic effects in univariable as well as multivariable analysis. The association of wild-type NER genotypes with better PFS and higher susceptibility to treatment-related toxic effects was confirmed in haplotype analysis.

Conclusions: Our results suggest that polymorphisms in NER pathway influence platinum-treatment efficacy and toxicity; therefore, these should be further evaluated as potential markers for the prediction of clinical outcome in patients with MM.

Key words: DNA repair polymorphisms, glutathione S-transferases, malignant mesothelioma, pharmacogenetics, platinum

introduction

Malignant mesothelioma (MM) is a rare and aggressive tumor, which arises from mesothelial surfaces of the pleura and less frequently from peritoneum, and is causally associated with previous asbestos exposure [1]. Due to the long latent period between exposure and disease, the rapid increase in the number of MM cases is not expected to stabilize before 2020 [2]. The annual incidence of MM in Slovenia has more than doubled over the past 15 years and ~1–2 cases per 100 000 has been registered [3]. At the moment, there is no standard treatment for early-stage MM [4]. Because multimodality approaches have been shown to improve survival only in selected cases [5], the majority of patients with MM are treated with systemic chemotherapy. Platinum-based combination chemotherapy is the most effective [6]. Cisplatin combination with pemetrexed has become the standard chemotherapy [7]; however, combination with gemcitabine has similar efficacy [8].

Platinum agents covalently bind to DNA, form intrastrand DNA adducts or interstrand cross-links, and lead to replication and transcription arrest. DNA adducts are recognized and repaired by nucleotide excision repair (NER) mechanisms. NER proteins such as xeroderma pigmentosum group D (XPD) and excision repair cross-complementation group 1 (ERCC1) are polymorphic. Two common nonsynonymous XPD single nucleotide polymorphisms (SNPs), Asp312Asn and Lys751Gln, were associated with reduced lymphocyte messenger RNA (mRNA) expression is not very clear [14, 15].

Besides enhanced DNA repair, resistance to platinum is also attributable to enhanced detoxification of platinum-based drugs by glutathione S-transferases (GSTDs) pi (GSTD1), mu (GSTM1), and theta (GSTT1) [16, 17]. Two common SNPs, Ile105Val and Ala114Val, in GSTD1 gene decrease enzymatic activity [18, 19]. Deletion polymorphisms resulting in complete loss of enzymatic activity in homozygous carriers have been described in GSTM1 and GSTT1 [20].
Genetic variability influencing the activity of enzymes involved in these cellular defense pathways may lead to significant variations in treatment response and occurrence of adverse drug reactions to platinum-based chemotherapeutic drugs. Several studies have found correlations between these putatively functional SNPs and clinical outcome in patients treated with platinum-based chemotherapy for non-small-cell lung cancer (NSCLC) [21–23], colorectal cancer (CRC) [24, 25], ovarian cancer [26], osteosarcoma [27], esophageal cancer [28], or testicular cancer [29], although their findings were inconsistent. The role of NER and GST polymorphisms on treatment outcome in patients with MM has not been well established.

Therefore, the aim of our study was to evaluate the influence of NER and GST polymorphisms on tumor response, survival, and treatment-related toxicity in patients with MM treated with platinum-based chemotherapy and those not treated with platinum agents.

materials and methods

patients

Our study group consisted of 133 patients with histologically confirmed MM, diagnosed at the University Clinic of Pulmonary and Allergic Diseases in Gornik, Slovenia, and at the University Clinical Centre Maribor, Slovenia, between years 1997 and 2010. Demographic, treatment, and clinical data were obtained from the medical records or during the clinical interview. Characteristics of the entire cohort are presented in supplemental Table S1 (available at Annals of Oncology online).

All patients gave their written informed consent to participate in the study. The study was approved by the Slovenian Ethics Committee for Research in Medicine (approval ref. no. 04/02/09) and was carried out according to the Declaration of Helsinki.

treatment

The assessment of extended disease, treatment, outcome, and follow-up of all patients with MM was carried out at the Institute of Oncology Ljubljana, Slovenia. Patients with MM were considered for inclusion in the study if they were treated with one of the platinum-based regimens as a part of the first-line therapy (supplemental Table S2, available at Annals of Oncology online). We also included a group of patients not treated with platinum agents, receiving non-platinum-based chemotherapy (gemcitabine plus vincristine, doxorubicin plus ifosfamide, gemcitabine monotherapy) or best supportive care (BSC).

response, survival, and toxicity assessment

Tumor response was evaluated according to the modified RECIST [30]. Progression-free survival (PFS) time was defined as time from the day of diagnosis to the day of documented disease progression or death from any cause, while overall survival (OS) time was defined as time from the day of diagnosis to the death from any cause. Patients without documented progression or death at the time of the final analysis were censored at the date of the last follow-up.

Hematologic (anemia, leukopenia, neutropenia, and thrombocytopenia) and non-hematologic (nephrotoxicity defined by serum creatinine level, alopecia, and nausea/vomiting) toxic effects were evaluated according to the National Cancer Institute—Common Toxicity Criteria, version 2.0. Toxic effects of grade ≥ 2 were considered as clinically relevant. Thrombocytopenia and nephrotoxicity were categorized only as present or absent because there were no occurrences of grade ≥ 3 toxicity.

DNA extraction and genotyping

Tumor tissue specimens or peripheral blood samples were collected at the time of diagnosis. Genomic DNA from formalin-fixed and paraffin-embedded (FFPE) tumor tissue was extracted as previously described [31]. For extraction of genomic DNA from frozen whole-blood samples, Qiagen FlexiGene kit (Qiagen, Hilden, Germany) was used.

Genotyping of XPD Asp312Asn (rs1799753), XPD Lys751Gln (rs13181), ERCC1 19007T>C (rs11615), and ERCC2 8092C>A (rs321986) was carried out using a fluorescence-based competitive allele-specific (KASPar®) assay according to the manufacturer’s instructions (KBiosciences, Herts, UK). GSTP1 Ile105Val (rs1695) and Ala114Val (rs1138272) polymorphisms were determined as described previously [32]. GSTM1 and GSTT1 copy numbers were determined by quantitative real-time PCR using TaqMan® Gene Copy Number Assays (AB assays Hs02995872_cn and Hs01731033_cn, respectively; Applied Biosystems, Foster City, CA) according to the manufacturer’s instructions using RNase P as an endogenous control. Relative quantification was carried out using CopyCaller™ Software (Applied Biosystems).

statistical analyses

For the comparison of categorical data distribution, chi-square and Fisher’s exact tests were used. Numerical and survival data were compared between groups using t-test and log-rank test, respectively. Hardy–Weinberg equilibrium (HWE) was assessed using standard chi-square test.

A dominant genetic model was used in all statistical analyses. The influences of genetic polymorphisms on tumor response and the occurrence of treatment-related toxic effects were examined by univariable logistic regression analysis to calculate odds ratios (ORs) and their 95% confidence intervals (CIs). Survival curves were estimated using the Cox proportional hazards model and the hazard ratio (HR) with the 95% CI was determined.

All significant correlations were further examined in multivariable regression analysis adjusted for clinical variables with evidence of prognostic or predictive impact. All statistical analyses were carried out by SPSS for Windows version 16.0.1 software (Statistical Package for the Social Sciences, Chicago, IL).

On the basis of all NER genotypes data, haplotypes were reconstructed and analyzed using the Thesias program [33, 34].

The level of significance for all statistical analyses was set at P = 0.050.

results

patients

In total, 133 patients with MM were assessable for analysis. Among them, 97 patients received platinum-based chemotherapy (detailed in supplemental Table S2, available at Annals of Oncology online), whereas the others were not treated with platinum agents (n = 36). Patients’ characteristics for both groups are summarized in Table 1. Patients not treated with platinum were significantly older (P = 0.016), had higher frequency of non-epithelioid histology (P = 0.017), and had shorter median PFS time (P < 0.001), as well as shorter median OS time (P < 0.001). There were no significant differences in all other patients’ characteristics (Table 1).

Genotype frequencies for the entire cohort are presented in supplemental Table S3 (available at Annals of Oncology online). Genotypes of all the eight polymorphisms were in HWE equilibrium (P > 0.05) for any polymorphism. The genotype frequencies were not significantly different between treatment groups (P > 0.050 for any polymorphism).
We observed no statistically significant differences in genotype frequency distribution between tumor and blood samples \( (P > 0.050 \text{ for any polymorphism}) \) and also no deviations from HWE for any polymorphism in either group \( (P > 0.050 \text{ for any polymorphism}) \).

**tumor response analysis**

Patients who underwent surgical resection of tumor before chemotherapy were not assessed in tumor response analysis. Among 89 assessable patients, there were 5 complete (5.6%) and 43 partial responders (48.3%), together accounting for an overall response rate of 53.9%. Stable disease was observed in 35 patients (39.3%) and 6 had progressive disease (6.7%). No significant correlations were found between investigated polymorphisms and the proportion of patients who achieved complete or partial response.

**survival analysis**

The influence of NER and GST polymorphisms on PFS and OS was investigated in both platinum-treated patients \( (n = 97) \) and those not treated with platinum agents \( (n = 36) \) by univariable Cox proportional hazards model (supplemental Table S4, available at *Annals of Oncology* online).

Wild-type XPD 751Lys/Lys and ERCC1 8092C/C genotypes were significantly associated with reduced hazard of disease progression in platinum-treated patients \( (HR = 2.01, 95\% \text{ CI } 1.18–3.41, P = 0.010, \text{ and } HR = 1.81, 95\% \text{ CI } 1.15–2.86, P = 0.011, \text{ respectively; Figure 1} \) but had no effect in patients not treated with platinum. In the latter group, a significant association between GSTT1 polymorphism and PFS was observed \( (HR = 2.55, 95\% \text{ CI } 1.04–6.24, P = 0.041) \), indicating a correlation between homozygous GSTT1 gene deletion and worse PFS. Other polymorphisms were not associated with PFS in any of the treatment groups.

Clinical variables with evidence of prognostic or predictive impact \( \text{[age, sex, asbestos exposure, smoking status, performance status, site of cancer, histological type, TNM (tumor–node–metastasis) stage, type of treatment, chest pain, performance status, site of cancer, histological type, TNM (tumor–node–metastasis) stage, type of treatment, chest pain, } \) were also examined for their influence on PFS. In Cox proportional hazards analysis, the following clinical variables independently influenced PFS in the entire cohort: non-epithelioid histology \( (HR = 2.76, 95\% \text{ CI } 1.83–4.18, P < 0.001), \) TNM stage \( (HR = 1.28, 95\% \text{ CI } 1.05–1.57, P = 0.014), \) and LDH level at the time of diagnosis \( (HR = 1.01, 95\% \text{ CI } 1.00–1.02, P = 0.006). \) In a multivariable model adjusted for these clinical variables, only ERCC1 8092C>A remained significantly associated with PFS \( (HR = 1.69, 95\% \text{ CI } 1.04–2.74, P = 0.034). \)

None of the investigated polymorphisms influenced OS, regardless of the treatment group (supplemental Table S4, available at *Annals of Oncology* online).

**toxicity analysis**

The influence of NER and GST polymorphisms on treatment-related toxic effects in platinum-treated patients \( (n = 94) \) is shown in Table 2. None of the investigated polymorphisms influenced the occurrence of grade ≥2 anemia, grade ≥2 neutropenia, or nephrotoxicity. Thrombocytopenia was significantly more frequent among patients with wild-type XPD 312Asp/Asp genotype than carriers of at least one 312Asn allele \( (25.7\% \text{ versus } 5.0\% \text{ of patients, } P = 0.008) \). Likewise, patients with wild-type ERCC1 8092C/C genotype developed thrombocytopenia more frequently compared with patients with at least one polymorphic 8092A allele \( (20.4\% \text{ versus } 4.3\% \text{ of patients, } P = 0.032) \). The occurrence of grade 2 alopecia was more common among patients with wild-type XPD 312Asp/Asp genotype relative to carriers of at least one polymorphic
312Asn allele (67.6% versus 36.7% of patients, \(P = 0.005\)) as well as among patients with wild-type \(ERCC1\) 8092C/C genotype relative to carriers of at least one polymorphic 8092A allele (60.4% versus 34.8% of patients, \(P = 0.014\)). Additionally, grade \(\geq 2\) nausea/vomiting occurred more frequently in patients with wild-type \(ERCC1\) 8092C/C genotype compared with patients with polymorphic 8092C/A or 8092A/A genotype (46.9% versus 21.7% of patients, \(P = 0.011\)). Patients with homozygous \(GSTM1\) gene deletion developed significantly less grade \(\geq 2\) leukopenia compared with carriers of at least one functional allele (30.9% versus 51.3% of patients, \(P = 0.048\)). Other polymorphisms were not associated with treatment-related toxic effects.

The identified associations were examined in multivariable logistic regression model adjusted for clinical covariates (sex, Eastern Cooperative Oncology Group (ECOG) performance status \(\geq 2\), number of first-line chemotherapy cycles, and type of first-line chemotherapy regimen considered as gemcitabine–

![Figure 1](image-url)

**Figure 1.** Cox proportional hazards model of progression-free survival (PFS) in the function of \(XPD\) Lys751Gln genotype (left) and \(ERCC1\) 8092C>A genotype (right) for platinum-treated patients with malignant mesothelioma (\(n = 97\)). PFS curves were estimated for patients with wild-type (full line) and polymorphic (dashed line) genotype.

**Table 2.** The influence of NER and GST genotypes on occurrence of treatment-related toxic effects in platinum-treated patients with malignant mesothelioma (\(n = 94\)).

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Grade (\geq 2) leukopenia</th>
<th>Thrombocytopenia</th>
<th>Grade (\geq 2) alopecia</th>
<th>Grade (\geq 2) nausea/vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>(XPD) Asp312Asn</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Asp/Asp &amp; Asp/Asn &amp; Asp/Asn</td>
<td>0.66 (0.28–1.53)</td>
<td>0.15 (0.04–0.61)</td>
<td>0.008</td>
<td>0.28 (0.11–0.67)</td>
</tr>
<tr>
<td>(ERCC1) 8092C&gt;A</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>T/T &amp; C/C &amp; C/A &amp; A/A</td>
<td>1.04 (0.43–2.52)</td>
<td>1.53 (0.38–6.09)</td>
<td>0.549</td>
<td>1.11 (0.46–2.65)</td>
</tr>
<tr>
<td>(GSTP1) Ile105Val</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Ile/Ile &amp; Val/Val &amp; Ile/Val &amp; Val/Val</td>
<td>1.44 (0.61–3.39)</td>
<td>1.39 (0.39–4.98)</td>
<td>0.615</td>
<td>0.95 (0.42–2.18)</td>
</tr>
<tr>
<td>(GSTP1) Ala114Val</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Ala/Ala &amp; Ala/Val &amp; Val/Val</td>
<td>0.61 (0.27–1.42)</td>
<td>0.18 (0.04–0.86)</td>
<td>0.032</td>
<td>0.35 (0.15–0.81)</td>
</tr>
<tr>
<td>(GSTM1) CNV</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1/1 &amp; 1/0 &amp; 0/0</td>
<td>0.43 (0.18–0.99)</td>
<td>0.048</td>
<td>1.05 (0.26–4.26)</td>
<td>0.946</td>
</tr>
<tr>
<td>(GSTT1) CNV</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1/1 &amp; 1/0 &amp; 0/0</td>
<td>1.25 (0.48–3.25)</td>
<td>0.642</td>
<td>1.46 (0.41–5.23)</td>
<td>0.562</td>
</tr>
</tbody>
</table>

Data on treatment-related toxicity missing for three patients. Bold characters indicate statistically significant results.

*Genotyping data missing for one patient.

CI, confidence interval; CNV, copy number variation; GST, glutathione S-transferase; NER, nucleotide excision repair; OR, odds ratio.
platinum combination based or other) predictive for the occurrence of treatment-related toxic effects in our study. Among all the investigated associations, only the occurrence of thrombocytopenia remained significantly influenced by both XPD Asp312Asn (OR = 0.19, 95% CI 0.04–0.87, P = 0.032) and ERCC1 8092C>A (OR = 0.18, 95% CI 0.03–0.96, P = 0.044) polymorphisms.

**haplotype analysis**

Because XPD and ERCC1 SNPs that significantly influenced treatment outcome in platinum-treated patients were in linkage disequilibrium (D' for XPD Lys751Gln–XPD Asp312Asn–ERCC1 8092C>A–ERCC1 19007T>C was 1–0.61–0.47–0.43), haplotype analysis was carried out to evaluate their combined effect. Among fourteen 4-SNP (XPD Lys751Gln–XPD Asp312Asn–ERCC1 8092C>A–ERCC1 19007T>C) haplotypes, only four had frequencies >5% and together accounted for 70.3% of the variability in the patients with MM. None of the common haplotypes influenced tumor response (P > 0.50) for any haplotype. However, we found a significant association between polymorphic CAAC haplotype and PFS (P = 0.005), as well as OS (P = 0.041) (Table 3).

NER haplotypes also influenced treatment-related toxic effects. Polymorphic CAAC haplotype nonsignificantly reduced odds of any treatment-related toxic effects; however, the association with occurrence of grade ≥2 nausea/vomiting was statistically significant (OR = 0.28, 95% CI 0.08–0.98, P = 0.046). Carriers of CGCT haplotype were more likely to develop thrombocytopenia than those with wild-type AGCT haplotype (OR = 11.32, 95% CI 2.07–62.07, P = 0.005).

**discussion**

The present study investigated associations of NER and GST polymorphisms with efficacy and toxicity of platinum-based chemotherapy in patients with MM.

Our study showed no associations between any investigated polymorphism and tumor response or OS. In contrast, XPD 751Lys/Lys and ERCC1 8092C/C wild-type genotypes were significantly associated with better PFS in platinum-treated patients but not in those not treated with platinum agents. ERCC1 8092C/C genotype remained significantly associated with PFS even after taking into account clinical variables, indicating its independent influence on treatment efficacy. Our results are in agreement with the recent publication that showed no association of ERCC1 19007T>C polymorphism with tumor response or survival in MM [36]. However, other NER and GST polymorphisms were not assessed in this single study published so far on pharmacogenetics of platinum-based treatment in MM. The association of wild-type XPD 751Lys and ERCC1 8092C alleles with better survival upon platinum-based treatment was shown in NSCLC [21–23], CRC [24, 37], ovarian cancer [26], and osteosarcoma [27]. Similar to our observations, Okuda et al. [22] reported better prognosis of patients with NSCLC with ERCC1 8092C/C genotype treated with platinum-based chemotherapy and found no association of this genotype with survival in those not treated with platinum. Other studies found no associations of XPD and ERCC1 polymorphisms with treatment outcome [38, 39] or even reported an opposite effect of wild-type alleles [28]. Our results indicate that patients with XPD 312Asp/Asp or ERCC1 8092C/C wild-type genotype were more likely to develop treatment-related toxic effects. In multivariable analysis after adjustment for clinical predictors, wild-type NER genotypes remained significantly associated with occurrence of thrombocytopenia. Most studies published to date observed no associations between XPD and ERCC1 polymorphisms and occurrence of treatment-related toxic effects; however, conflicting results were reported in ovarian cancer [40] and NSCLC [41]. This may indicate that the biological significance of SNPs is tissue dependent, as has been a case with other biomarkers [42].

Finally, haplotype analysis carried out in our study confirmed the association of wild-type NER genotypes with better PFS and higher susceptibility to treatment-related toxic effects. To our knowledge, only one study investigated the influence of the combined effect of XPD and ERCC1 polymorphisms on platinum treatment outcome in esophageal cancer [28], but they reported an association of wild-type AGCT haplotype with shorter survival. Due to divergent assumptions about influence of the investigated NER polymorphisms on protein expression or DRC, their functionality is questionable. The exploratory haplotype analysis carried out in our study may indicate that some other functional polymorphism in linkage disequilibrium with the investigated polymorphisms influences the survival of patients with MM treated with platinum-based chemotherapy.

In the past years, several studies also investigated the role of GST polymorphisms in response to platinum-based therapy. Contrary to our findings, many of them showed an association of GSTP1 105Val variant with treatment outcome [40, 43]. The putative impact of GSTM1 and GSTT1 gene deletions on improved survival in platinum-treated patients [29, 44] has not been confirmed in our study. Significant association between GSTT1 polymorphism and PFS was observed only in patients not treated with platinum agents. Similar to other studies, we observed an association between GSTM1 null genotype and lower frequency of treatment-related leukocytopenia [40].

Although our study had some limitations, arising from its retrospective nature, we took special care to account for possible factors that could influence our results. First, our cohort was heterogeneous regarding clinical and treatment
characteristics. Nevertheless, all clinical variables that might have affected survival or toxicity were taken into consideration in multivariable analysis. Patients with MM who were not treated with platinum agents had similar performance status and TNM stage compared with platinum-treated patients but had significantly worse survival. The majority of them received only BSC as they were mostly elderly people, had high comorbidity, or refused the chemotherapy. Most of them were also diagnosed and treated before the year 2003, when the first randomized studies showed that systemic chemotherapy prolonged the survival of patients with MM [7, 45].

Secondly, the use of different DNA sources for genotyping analysis might lead to misinterpretation of our results, but we observed no differences in genotype frequency distribution between tumor and blood samples. Additionally, genotype frequency distribution did not deviate from HWE in tumor samples, indicating no loss of heterozygosity for any of the investigated genes. Our observations were also in good agreement with other studies that showed strong concordance of XPD and ERCC1 genotypes between normal samples and FFPE CRC tumor tissue [46, 47]. Similarly, good agreements of GSTP1, GSTM1, and GSTT1 genotypes were reported between paired acute myeloid leukemic and somatic cells [48].

Although our cohort of patients with MM was relatively small, our study was not biased by genetic heterogeneity because all the patients were recruited in a geographic area with an ethnically homogeneous population [49]. The discrepancies in clinical data collection procedure were minimized, as treatment, outcome assessment, and follow-up were centralized for all included patients with MM.

Our results are in concordance with the only study investigating the role of ERCC1 19007T>C polymorphism in MM treatment response and survival that has been recently published [36], but our findings should be validated in a prospective study with a larger group of patients with MM.

In conclusion, single SNP as well as haplotype analyses carried out in our study showed an association of wild-type XPD and ERCC1 genotypes with improved survival and increased level of treatment-related toxic effects, suggesting an important role of NER genes in platinum-treatment outcome. Therefore, XPD and ERCC1 genotyping might serve as a genetic marker of platinum-based chemotherapy efficacy and toxicity in patients with MM.

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disclosure

The authors declare no conflict of interest.

references


