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Phase II Study of Satraplatin and Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer: A Pharmacogenetic Assessment of Outcome and Toxicity

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Abstract

Genetic polymorphisms in DNA repair enzymes (excision repair cross-complementing group 1 [*ERCCI*] and x-ray cross-complementing group 1 [*XRCCI*]) may predict treatment outcome and response to platinum-based treatment. Twenty-four patients were enrolled in this single-arm study to assess the association between *ERCCI* and *XRCCI* gene variants and treatment outcomes with satraplatin in patients with docetaxel-refractory metastatic castration-resistant prostate cancer.

Background—We assessed the effect of excision repair cross-complementing group 1 (*ERCCI*) and x-ray cross-complementing group 1 (*XRCCI*) gene polymorphisms on treatment outcomes with satraplatin and prednisone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel-based therapy.

Patients and Methods—Twenty-four patients were enrolled in this single arm study. The primary objective was to determine if the presence of *ERCCI* Asn118Asn (N118N, 500C>T, rs11615) and *XRCCI* Arg399Gln (R399Q, 1301G>A, rs25487) genetic variants might be associated with an impact on progression-free survival (PFS); secondary objectives included overall response, survival, and toxicity.

Results—After population stratification by race, white patients carrying heterozygous or variant genotypes at the *ERCCI* C>T locus had a >3-fold longer median PFS (5.8 vs. 1.8 months; $2P = .18$, adjusted) and 5-fold longer median overall survival (OS) (15.7 vs. 3.2 months; $2P = .010$, adjusted) than did patients carrying only wild-type alleles. For the *XRCCI* G>A variant, without regard to race, patients carrying the wild-type GG alleles had a longer PFS (9.3 months) than those

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Disclosure

The authors have stated that they have no conflicts of interest.

carrying GA or AA alleles (2.7 months; $2P = .02$). Similarly, those carrying GG alleles did not reach median OS, whereas those carrying GA or AA alleles had a median OS of 9.6 months ($2P = .12$, adjusted). Multivariable analysis by using Cox proportional hazards modeling demonstrated that only *XRCC1* was associated with PFS.

Conclusions—To our knowledge, this is the first prospective study to date in patients with metastatic castration-resistant prostate cancer that describes predictive germline polymorphisms of *ERCC1* and *XRCC1* for assessing the clinical activity of satraplatin.

Keywords

ERCC1; Genotyping; Prostate cancer; Satraplatin; *XRCC1*

Background

Prostate cancer is the second leading cause of cancer deaths among men in the United States, with an estimated incidence of 241,740 new cases diagnosed and 28,170 patients dying in 2012.¹ Men with symptomatic metastatic castration-resistant prostate cancer (mCRPC) are treated with docetaxel and prednisone as the standard of therapy, which have demonstrated an approximate 3-month median survival advantage compared with mitoxantrone chemotherapy.²⁻⁴ For patients with postdocetaxel progressive disease, cabazitaxel⁵ and abiraterone acetate⁶ have recently been approved as second-line treatment options for this difficult-to-treat population. Despite these additions to the treatment armamentarium, the duration of response is generally short lived, with a modest survival benefit; mCRPC remains incurable, and novel therapeutic approaches are in demand, especially in the postdocetaxel setting.

Satraplatin (bisacetato-ammine-dichloro-cyclohexylamine platinum IV; JM-216) is an oral, third-generation platinum analogue that has preclinical activity in prostate cancer and tumor cell lines resistant to cisplatin, taxanes, or anthracyclines.⁷⁻¹⁰ In a phase II trial, satraplatin demonstrated activity in castration-resistant prostate cancer (CRPC), with myelosuppression being the most common and significant toxicity.¹¹ The low toxicity of satraplatin and promising clinical activity in CRPC provided support for a randomized phase III trial of satraplatin plus prednisone vs. prednisone alone as first-line treatment of patients with mCRPC.¹² Despite the early termination of the study by the sponsor after 50 patients were enrolled, a significant increase in progression-free survival (PFS) (5.2 vs. 2.5 months; $2P = .023$) was observed; however, the 3-month increase in median overall survival (OS) was not statistically significant, perhaps owing to the small sample size.¹² Nonetheless, these encouraging results led to further investigation of this regimen in a large randomized phase III SPARC (Satraplatin and Prednisone Against Refractory Prostate Cancer) trial¹³ in men with mCRPC who experienced progression after one prior chemotherapy regimen. The study results demonstrated that, although satraplatin delayed progression of disease and pain in patients, it did not provide a significant OS benefit in this unselected patient population; as such, satraplatin has not received regulatory approval. Although further development of satraplatin in phase III trials has ceased after the results of the SPARC trial, given the favorable toxicity profile and convenient oral administration, satraplatin may warrant development in the setting of tailored therapy to selected patients who would likely benefit from platinum-based therapy.

Results of many studies have indicated that polymorphisms of DNA repair genes may influence platinum-based treatment efficacy in a cancer-specific manner. Satraplatin forms platinum-DNA adducts and crosslinks¹⁴ but is not susceptible to some cisplatin resistance mechanisms.¹⁵ One of the mechanisms that bring about resistance to platinum-based chemotherapy involved removal of the platinum-DNA adducts by DNA repair pathways

called nucleotide excision repair (NER) and base excision repair (BER) pathways. DNA repair enzymes, such as excision repair cross-complementing 1 (*ERCC1*) and x-ray cross-complementing group 1 (*XRCC1*), are important players in NER and BER pathways, respectively. Single nucleotide polymorphisms in these genes cause impaired NER and BER capability and have been reported in various types of cancer, including head and neck squamous cell carcinoma,¹⁶ non-small-cell lung carcinoma,¹⁷⁻²¹ and ovarian carcinoma.²²⁻²⁵ These variants predicted treatment outcome and response to platinum-based treatment. The primary objective of this single-arm study was to determine if the presence of *ERCC1* Asn118Asn (N118N, 500C>T, rs11615) and *XRCC1* Arg399Gln (R399Q, 1301G>A, rs25487) variant gene polymorphisms, conferring interindividual variation in damage repair pathways, might be associated with an impact on the PFS of patients with mCRPC. Secondary objectives included measuring overall response, toxicity, and determining the association between genotype expression and OS.

Patients and Methods

Patient Selection

Patients were considered eligible if they had (a) histologic confirmation of prostatic adenocarcinoma; (b) mCRPC with radiographic evidence of disease with progression defined as an increase in radiographic lesions and/or prostate-specific antigen (PSA) level increasing on successive measurements; (c) received prior docetaxel-based chemotherapy regimen but may have had no more than one previous cytotoxic chemotherapy regimen; (d) Eastern Cancer Oncology Group status of 0, 1, or 2; (e) life expectancy longer than 3 months; and (f) adequate bone marrow, hepatic, and renal functions. Patients were excluded for prior platinum therapy, additional malignancy, or significant radiotherapy (>30% of the bone marrow exposed to radiation or any previous treatment with bone-seeking radioisotope). Concomitant bisphosphonate therapy was allowed. All the patients gave written informed consent in accordance with federal, state, and institutional guidelines, and the National Cancer Institute Institutional Review Board approved the study.

Study Design

This was a phase II trial that used a single-stage, single-arm design, with the primary objective of determining if the presence of a polymorphism in genes involved in the DNA damage repair pathway may be associated with an impact on the PFS of patients with mCRPC. The particular polymorphisms of interest, in *ERCC1* and *XRCC1*, have a wild-type (CC) prevalence of 21% in whites and 76% in African Americans and a wild-type (GG) prevalence of 68% in whites and 89% in African Americans, respectively.²⁶

Treatment

Satraplatin 80 mg/m² was administered orally (p.o.) once daily (fasting) on days 1 to 5 every 35 days. Prednisone (prednisolone) 5 mg p.o. was administered twice a day (b.i.d.) throughout the 35-day cycle. Antiemetic prophylaxis (granisetron 1 mg p.o., b.i.d.) was administered daily 30 to 60 minutes before and 8 hours after each satraplatin dose.

Assessment

The patients were evaluated in the clinic every cycle (5 weeks), and radiographic assessments by using computed tomography and bone scintigraphy were obtained every 2 cycles. Blood tests, including complete blood cell count, chemistry, and PSA level, were obtained at each cycle visit. The patients were evaluated based on response evaluation criteria in solid tumors every 2 cycles. The patients were permitted to stay in the study unless (a) there is radiologic disease progression, (b) intercurrent illness that required

cessation of satraplatin, (c) the patient decided to withdraw from the study, or (d) there was unacceptable toxicity. Progressive disease in patients with only bone metastasis was defined as the development of new lesions or clinical signs of progression; response was defined as the disappearance of any bone lesions. Patients who had increasing PSA levels could stay in the study if they did not meet the above exclusion criteria. The PSA level response rate was defined as the proportion of patients with a decrease of $\geq 50\%$ in the PSA concentration from the pretreatment baseline PSA value, which was confirmed by a second value at least 4 weeks after the first value with no other evidence of disease progression according to the criteria by Bubley et al.²⁷

Adverse events evaluation and the dose adjustments of satraplatin were based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Briefly, patients found to have grade 1 toxicity had no dose adjustment or interruptions. Satraplatin dose was decreased by 25% for persistent grade 2 nausea, vomiting, or diarrhea. Satraplatin doses were delayed 1 week or decreased in the event of hematologic toxicity (absolute neutrophil count, $500/\mu\text{L}$; platelets, $25,000/\mu\text{L}$, or neutropenic fever) or gastrointestinal toxicity (grade 3 nausea, vomiting, or diarrhea); up to 2 dose delays or reductions of satraplatin were allowed (80 to 60 mg/m^2 and 60 to 40 mg/m^2). One dose reduction of prednisone to 5 mg once daily was allowed for grade 3 hyperglycemia or other prednisone-related toxicity. To continue treatment, the patients had to have an absolute neutrophil count $1500/\mu\text{L}$, platelets $100,000/\mu\text{L}$, and nonhematologic toxicities attributed to study drug resolved to baseline or grade 1 (except alopecia) or grade 2 for pain.

Genotyping: Sample Collection and Analysis

Approximately 10 mL of blood was drawn by using a 10-mL EDTA tube for DNA extraction. Genomic DNA was extracted from serum or white blood cell buffy coat layers of whole blood of patients according to the manufacturer's instructions by using the QiaAMP DNA Blood Kit (Qiagen, Valencia, CA). Polymerase chain reaction (PCR) was performed by using the platinum Taq PCR Kit (Invitrogen, Carlsbad, CA) with gene-specific primers. PCR was denatured at 94°C for 5 minutes, followed by denaturation at 94°C for 30 seconds, annealing at optimal temperature for each pair of primers for 30 seconds, and synthesis for 30 seconds at 72°C for 40 cycles; the final extension was carried out at 72°C for 7 minutes. Primers and PCR conditions used in this study will be provided per request. Direct nucleotide sequencing PCR was conducted by using the Big Dye Terminator Cycle Sequencing Ready Reaction kit V3.1 (Applied Biosystems, Foster City, CA) and an ABI Prism 3130 Genetic Analyzer by using the manufacturer's instructions.

The synonymous *ERCC1* N118N transition ($500\text{C}>\text{T}$; rs11615) and the nonsynonymous *XRCC1* R399Q ($\text{G}>\text{A}$) variant (rs25487) were in Hardy-Weinberg equilibrium in non-Hispanic whites ($2P>.58$; $n=15$) with a variant allele frequency of 0.63 and 0.43, respectively. However, one of these patients (carrying $500\text{C}>\text{T}$ var/var, and R399Q wt/var) withdrew from the study before therapy and thus was not evaluable. African Americans ($n=4$) had a variant allele frequency of 0.63 and 0.38, respectively, and there was a single Hispanic patient who was heterozygous for $500\text{C}>\text{T}$ and not evaluated for R399Q. Deviations from allele frequency determined in by Gao et al²⁶ were likely due to low numbers of patients who were genotyped in the present study.

Statistical Analysis

Hardy-Weinberg equilibrium was assessed by the χ^2 test. The objective of the analyses was to determine if the genotypes were associated with PFS, or with OS, after adjustment for the impact of prior treatment and clinical or demographic parameters. Univariate associations

between genotype or clinical parameters and PFS or OS were initially analyzed by using the Kaplan-Meier method, with statistical significance determined by the log-rank test. If the initial exploration demonstrated that combining groups would result in a stronger association with outcome, the subsequent *P* values were multiplied by 2 to account for the impact of the implicit testing undertaken to arrive at the final grouping. Those factors, which appeared to be associated with outcome with at least a potential trend in univariate analyses ($P < .15$ approximately), were further explored for their association with outcome by using Cox proportional hazards models. Except as stated above, all *P* values are 2-tailed and presented without adjustment for multiple comparisons. *ERCC1* (rs11615) and *XRCC1* (rs25487) genotypes were also compared with the types of toxicity that were noted in at least 3 patients and tested for the significance of the associations by using an exact Kruskal-Wallis test. Given the number of exploratory analyses performed, relationships between genotypes and toxicity were only considered significant when $2P < .01$, whereas $0.01 < 2P < 0.05$ suggested trends.

Results

Patient Characteristics

Twenty-four patients were enrolled between June 2008 and February 2011, and 23 of those patients were eligible and assessable for treatment outcome (1 patient was registered but never received therapy). The study demographics and baseline characteristics of all patients are presented in Table 1.

Response

Of the remaining 23 patients, 3 were nonevaluable for analysis of response. Three (15%) of the 20 evaluable patients had a $>50\%$ posttherapy decline in PSA level that was confirmed at least 1 month later. No objective responses were observed as defined by response evaluation criteria in solid tumors. Thirteen patients had stable disease as their best response, with the median duration of stable disease at 21 weeks (range, 5-22 weeks); 7 of these patients developed progression of disease; 4 patients did not show progressive disease on treatment but withdrew from the study as a result of toxicity or refusing further treatment; 2 patients currently remained on treatment, with stable disease at 52 and 74 weeks at the time that the data were evaluated. Progression of disease without evidence of response was noted in 7 patients. The median PFS was 6.0 months, and the median OS was 15.5 months.

Genotype vs. Response to Satraplatin and Survival Benefit

Univariate analysis revealed that baseline disease-related pain ($2P = .015$), lactate dehydrogenase (LDH) concentration ($2P = .0046$), and possibly hemoglobin level ($2P = .089$) and prior bisphosphonate treatment ($2P = .097$) were worthy of further exploration with respect to their role in PFS. In addition, hemoglobin ($2P = .071$), LDH concentration ($2P = .015$), possibly Gleason score ($2P = .10$, unadjusted; $2P = .20$, adjusted after grouping Gleason = 7 vs. Gleason = 8-10), and possibly alkaline phosphatase (ALP) ($2P = .13$) were worthy of further exploration with respect to their role in OS.

Neither PFS nor OS was associated with the *ERCC1* C>T(N118N) genotype when all patients were considered in univariate analyses (each $2P > .15$ in global evaluations). However, given that *ERCC1* N118N does not itself affect *ERCC1* expression²⁸ and appears to be a “passenger” marker by virtue of its strong linkage disequilibrium with other potential causative polymorphisms in whites,²⁹ the patient population was classified by race and reanalyzed within white patients; Hispanic and African American patients were not formally evaluated due to low numbers. Nonetheless, white patients carrying heterozygous or variant genotypes at the *ERCC1* C>T locus had a longer median PFS (5.8 months) than did patients

carrying only wild-type alleles (1.8 months), although this was nonsignificant ($2P = .18$, adjusted; Figure 1A). A statistically significant difference in OS among white patients also was observed ($2P = .010$, adjusted) in which patients carrying heterozygous or variant genotypes at the *ERCC1 C>T* locus had a longer median OS (15.7 months) than did patients carrying only wild-type alleles (3.2 months) (Table 2).

The *XRCC1* R399Q (G>A) variant was also explored with respect to survival endpoints irrespective of race. Patients carrying GG alleles had a longer PFS (9.3 months) than those carrying GA or AA alleles (2.7 months; $2P = .02$, adjusted) (Figure 1B). Similarly, those carrying GG alleles did not reach median OS, whereas those carrying GA or AA alleles had a median OS of 9.6 months ($2P = .12$, adjusted) (Table 2). The *XRCC1* R154W (rs1799782) variant was excluded from all analyses due to low variability (data not shown).

Multivariable analysis by Cox proportional hazards modeling was conducted for PFS when taking into consideration the aforementioned baseline factors and genotypes that were deemed worthy of further exploration on the basis of univariate analyses. Based on the univariate results, the following factors were selected for inclusion in the Cox model for PFS: *XRCC1* (GG vs. GA+AA), baseline pain, LDH level, hemoglobin level, and prior bisphosphonate concentration. By backward elimination, a model with *XRCC1* and baseline pain was selected (Table 3).

The following variables were selected for inclusion in the model for OS: *XRCC1* (GG vs. GA+AA), hemoglobin level, LDH level, Gleason score, and ALP level. By backward elimination, only ALP level and LDH level were related to OS, whereas a model was also produced that showed a marginal tendency for both *XRCC1* and hemoglobin to be jointly associated with survival (Table 3). Thus, whereas *ERCC1* (in whites only) and *XRCC1* genotypes were potentially related to PFS and/or OS in univariate analyses, only *XRCC1* rs25487 G>A was potentially shown to be associated with PFS after taking clinical factors into consideration, whereas both genotypes were of limited importance in OS when conventional baseline disease factors were taken into account.

Toxicities

All the patients who received treatment were analyzed for toxicity. The patients received a median of 4 cycles (range, <1 to 17 cycles). Of the 23 patients, 13 (57%) patients discontinued therapy because of disease progression, 3 (13%) patients due to toxicity, 4 (17%) patients because of a physician or patient decision but were not required by the protocol to stop, and 1 (4%) patient switched to an alternative treatment.

All the toxicities (grade 2, 3, and 4) that probably, possibly, and definitely were related to treatment that occurred in patients in the study are listed in Table 4. Hematologic toxicities were the major dose-limiting toxicity with leukopenia (39%, $n = 9$), anemia (30%, $n = 7$), and lymphopenia (30%, $n = 7$) being the most common grade 2 adverse events. The intensity of these events was usually mild to moderate. Most adverse events were of short duration and resolved without incident. Severe grade 3 toxicities included lymphopenia (26%), elevated ALP level (17%), and neutropenia (13%). The Cancer Institute Common Terminology Criteria for Adverse Events grade 4 toxicities were mainly hematologically related with thrombocytopenia (17%) and neutropenia (9%) being the most common adverse events. One patient died while in the study due to septic shock. Compared with other satraplatin trials, this study had a low incidence of gastrointestinal and constitutional symptoms.

Genotypes vs. Toxicity

The *ERCC1* 500C>T variant was related, or marginally nonsignificantly related, to the clinical grades of the following toxicities: anemia ($2P = .024$), neutropenia ($2P = .037$), and hypophosphatemia ($2P = .0035$) (Table 4). Stratification of the analysis to only include whites improved the association with anemia ($2P = .0092$) but decreased the significance of the relationships with neutropenia and hypophosphatemia ($2P = .051$ and $2P = .029$, respectively) and no new associations emerged. Contrary to expectations that the variant genotype (TT) would be linked to a “reduced DNA-repair” phenotype due to genetic linkage in whites and, therefore, experience more toxicity from platinum agents; all toxicities were actually more severe in carriers of the wild-type genotype (CC) than in carriers of variant alleles (TT). The *XRCC1* single nucleotide polymorphism was not related to any of the studied toxicities ($2P > .05$).

Discussion

ERCC1 is a critical gene in the NER pathway, whereas the codon 118 C/T polymorphism is the most widely studied genetic variant in this gene.³⁰⁻³² Analysis of results of some studies suggests that the polymorphism confers a reduction in *ERCC1* expression with less DNA repair (ie, a “reduced NER” phenotype) in whites and Asians,^{33,34} where linkage disequilibrium between N118N and other potential causative alleles is highest,²⁹ whereas cellular assays confirm that the *ERCC1* N118N single nucleotide polymorphism is not itself related to *ERCC1* phenotype.²⁸ Our laboratory also previously observed differences between whites and African Americans in the allelic frequencies of the *ERCC1* N118N polymorphism ($2P < .000001$); however, it is unlikely that this difference is meaningful if N118N is not linked to potential causative alleles in African Americans.^{26,29}

Therefore, analysis of our previous data suggested that the *ERCC1* N118N polymorphism would only be a relevant marker for *ERCC1* phenotype in the white population and not in African Americans. The “reduced NER phenotype” in whites may explain the improved survival rates in whites compared with African Americans in malignancies in which platinum compounds are important components of therapy, including lung, colorectal, ovarian, and other malignancies.^{22,35-44} We thus proposed that whites patients with prostate cancer who exhibit *ERCC1* variant alleles may have better response to a platinum agent such as satraplatin. Indeed, our trial results demonstrated that white patients carrying the heterozygous or variant genotypes at the *ERCC1* C>T locus had a substantially longer median PFS and several times longer median OS than did patients carrying only wild-type alleles. However, contrary to our hypothesis, variant carriers actually experienced reduced severity of anemia despite more drug treatment, thereby suggesting that reduced DNA repair capacity is favorable for this particular toxicity. Notably, the genotype was not related to any other toxicity caused by myelosuppression, albeit neutropenia was marginally nonsignificantly related. Thus, the relationship between anemia and the genotype is unclear at present and does not appear to be completely related to the myelosuppressive effects of satraplatin. Nevertheless, the analysis of the present data indicated that *ERCC1* 118 C/T or T/T might be a potential predictive marker of improved outcomes in patients with mCRPC treated with satraplatin and was consistent with reports of patients treated with platinum-based chemotherapy for non-small-cell lung cancer,⁴⁵ advanced-stage ovarian and primary peritoneal carcinoma,²³ pancreatic cancer,⁴⁶ ovarian cancer,^{22,24,47} and advanced colorectal cancer.⁴⁸ Although not all of these reports disclosed the patient population under study, all the trials in which patient data were available were either in Asians or primarily white populations. Therefore, it is highly likely that *ERCC1* N118N is only a marker of platinum response in these races in which N118N is strongly linked to other potential causative alleles.²⁹

XRCC1 is a critical component of BER, one of the major DNA repair pathways that repairs simple DNA base lesions. BER pathway is involved in the protection of cells from endogenous DNA damage induced by spontaneous hydrolysis and/or reactive oxygen species. Previous reports suggested that the *XRCC1* R399Q variant allele resulted in deficient DNA repair and increased DNA and chromo-some damage.^{49,50} Several studies have shown the association of *XRCC1* 399 wild-type G allele with an improved survival for patients who received platinum-based chemotherapy treated for pancreatic cancer,⁵¹ cervical cancer,^{52,53} gastric cancer,^{54,55} lung cancer,^{17,56} esophageal cancer,⁵⁷ colorectal cancer.⁵⁸ In the current trial, we found that patients carrying the GG alleles had a longer PFS and improved OS than those carrying the GA or AA alleles, and these results are in agreement with the above studies.

Conclusion

Since 2004, life-prolonging therapies for patients with mCRPC were limited to docetaxel-based regimens.^{3,4} Recently, the chemotherapy agent cabazitaxel⁵ and the targeted therapy abiraterone acetate⁶ received US Food and Drug Administration approval for men with disease progression after docetaxel chemotherapy. Although it appears that second-line treatment options for patients with mCRPC in the postdocetaxel setting have increased and outcomes have improved in the past couple of years, the duration of PFS and OS still remains relatively short. Several novel platinum-based agents have been investigated,⁵⁹ and, despite encouraging preclinical or early-phase results, some of these agents have underperformed in large randomized clinical trials, for example, satraplatin.¹³ Poor patient selection might be a contributing factor that led to these disappointing results and ongoing or future trials should attempt to focus on biomarker-based development of satraplatin for tailored therapy. For example, an ongoing phase 2 trial of men with progressive postdocetaxel mCRPC will evaluate the efficacy of satraplatin by using a gene expression model of BRCAness to be correlated with outcomes (<http://ClinicalTrials.gov> ID: NCT01289067). To the best of our knowledge, the current trial was the first prospective study that explored the association between genetic polymorphisms in DNA repair pathways and clinical outcomes of patients with mCRPC treated with satraplatin chemotherapy. Although *ERCC1* and *XRCC1* genotypes impacted PFS and/or OS in univariate analyses (although *ERCC1* was only important when analysis was restricted to whites, particularly for OS), only *XRCC1* rs25487 G>A was important with respect to PFS, and both genotypes were of limited importance in OS when conventional baseline disease factors were taken into account. Analysis of our results suggested that polymorphism of the *XRCC1* gene could be a useful surrogate marker of monitoring PFS and in selecting patients with mCRPC who would likely benefit from second-line satraplatin therapy. Further prospective studies that incorporate larger numbers of selected patients are warranted to validate its predictive value. Our study was limited by the small sample size and the limited number of minorities who had enrolled on the trial. Because allele frequencies of many single nucleotide polymorphism vary among different cancer populations and ethnicities, it would be necessary to evaluate *XRCC1* polymorphisms in a larger subset of African American patients in which mCRPC is more prevalent. Despite these limitations, our results were consistent with the literature and suggested that the rational development of satraplatin guided by optimal patient selection based on baseline clinical and/or molecular genetic factors may predict individuals who will likely benefit from treatment and subsequently enable its future addition to the mCRPC therapeutic armamentarium. Future challenges lie in determining the optimal sequence of the novel therapies, in-light of new second-line treatment options becoming available, especially those who have progressive disease after docetaxel therapy. It is equally important to identify patient subgroups based on robust predictive and prognostic biomarkers for treatment selection.

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Clinical Practice Points

- Although second-line treatment options for patients with mCRPC in the postdocetaxel setting have recently increased with improved outcomes, the duration of PFS and OS still remains relatively short; mCRPC remains incurable, and novel therapeutic approaches are in demand.
- Pharmacogenetic studies have indicated that polymorphisms of DNA repair genes may influence platinum-based treatment efficacy.
- Findings from this study demonstrate the effects of *ERCC1* and *XRCC1* gene polymorphisms on treatment outcomes with satraplatin and prednisone in patients with docetaxel-refractory mCRPC.
- Analysis of our results suggested that polymorphism of the *XRCC1* gene could be a useful surrogate marker of monitoring PFS and in selecting patients with mCRPC who would likely benefit from second-line satraplatin therapy.
- To our knowledge, this is the first prospective study in patients with mCRPC that describes predictive germline polymorphisms of *ERCC1* and *XRCC1* for assessing the clinical activity of satraplatin.

Figure 1. Kaplan-Meier Progression-Free and Overall Survival Curves According to Genotyping of (A) *ERCC1* N118N (C>T, restricted to white patients) and (B) *XRCC1* R399Q (G>A)

Table 1

Patient Demographics and Baseline Disease Characteristics (n = 23)

Patient Demographics and Clinical Characteristics	
Median (range) Age, y	65 (46.8-86.5)
65, %	52
Race, No. (%)	
White	15 (65)
African American	7 (31)
Hispanic	1 (4)
ECOG Performance Status, No. (%)	
0	3 (13)
1	17 (74)
2	2 (9)
Median (range) Gleason Score	8.5 (7-10)
Gleason Score, No. (%)	
8	16 (70)
7	6 (26)
Unclassified	1 (4)
Median (range) On-Study PSA Level, ng/mL	237 (0.04-1785)
Median (range) Hemoglobin Level, g/dL	11.8 (8.4-13.8)
Median (range) Lactate Dehydrogenase Level, U/L	192 (122-1716)
Median (range) Alkaline Phosphatase Level, U/L	110 (31-927)
Disease-Related Pain, No. (%)	9 (39)

Abbreviation: ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen.

Table 2

Univariate Associations Between Genotypes and PFS or OS

Genotypes	Median PFS		Median OS	
	Mo	2P Values ^a	Mo	2P Values ^a
<i>ERCC1</i> N118N (C>T)				
CC	1.8 ^b		3.2 ^b	
CT+TT	5.8 ^b	.09 (unadjusted); .18 (adjusted) ^b	15.7 ^b	.0049 (unadjusted); .010 (adjusted) ^b
<i>XRCC1</i> R399Q (G>A)				
GG	9.3		NR	
GA+AA	2.7	.01 (unadjusted); .02 (adjusted)	9.6	.061 (unadjusted); .12 (adjusted)

Abbreviations: *ERCC1* = excision repair cross-complementing-group 1; NR = not reached; OS = overall survival; PFS = progression-free survival; *XRCC1* = x-ray repair cross-complementing group 1.

^aLog-rank-test.

^bMedian durations and *P* values represent results from white patients only.

Table 3

Results of Cox Proportional Hazards Model Analysis for PFS and OS

Variable	2P Value	HR	95% HR Confidence Limits
PFS			
<i>XRCCI</i> GG	.030	10.99	1.27, 95.35
Baseline pain	.013	10.01	1.63, 61.52
OS			
LDH	.010	1.003	1.001, 1.005
ALP	.016	1.003	1.001, 1.006
OS Model Incorporating <i>XRCCI</i> GG			
<i>XRCCI</i> GG	.079	7.45	0.79, 70.09
Hemoglobin	.055	0.65	0.43, 1.01

Abbreviations: ALP = alkaline phosphatase; HR = hazard ratio; LDH = lactate dehydrogenase; OS = overall survival; PFS = progression-free survival; *XRCCI* = x-ray repair cross-complementing group 1.

Table 4

Toxicity vs. Genotypes: All Grade 2 to 4 Toxicities With an Attribution of at Least Possible Occurring in Patients Who Received Study Treatment (n = 23) Based on National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0)

Adverse Event	No. Patients (%)			2P Value, <i>ERCC1</i> (rs11615) ^a	2P Value, <i>XRCC1</i> (rs25487) ^a
	Grade 2	Grade 3	Grade 4		
Hematologic					
Anemia	7 (30)	2 (9)	1 (4)	0.024	0.97
Leukopenia	9 (39)	2 (9)	1 (4)	0.065	0.53
Lymphopenia	7 (30)	6 (26)	1 (4)	.58	.78
Neutropenia	3 (13)	3 (13)	2 (9)	.037	.70
Thrombocytopenia	6 (26)	1 (4)	4 (17)	.32	.54
Gastrointestinal					
Diarrhea	1 (4)	0 (0)	0 (0)		
Nausea	2 (9)	0 (0)	0 (0)		
Vomiting	1 (4)	0 (0)	0 (0)		
Constitutional					
Fatigue	3 (13)	0 (zero)	0 (0)	.33	.39
Anorexia	2 (9)	0 (0)	0 (0)		
Laboratory Abnormalities					
Elevated alkaline phosphatase level	0 (0)	4 (17)	0 (0)	.64	.54
Hypoalbuminemia	4 (17)	0 (0)	0 (0)	1.00	1.00
Hypokalemia	0 (0)	1 (4)	0 (0)		
Hypophosphatemia	1 (4)	2 (9)	0 (0)	.0035	1.00
Increased liver enzymes	1 (4)	0 (0)	0 (0)		
Infections					
Urinary	2 (9)	0 (0)	0 (0)		
Septic shock	0 (0)	0 (0)	1 (4)		
Renal Failure					
	0 (0)	1 (4)	0 (0)		
Hypertension					
	1 (4)	0 (0)	0 (0)		
Hypotension					
	0 (0)	0 (0)	1 (4)		
Dyspnea					
	0 (0)	1 (4)	0 (0)		
Stomatitis					
	1 (4)	0 (0)	0 (0)		

Adverse Event	No. Patients (%)			2P Value, <i>XRCCI</i> (rs11615) ^a	2P Value, <i>XRCCI</i> (rs25487) ^a
	Grade 2	Grade 3	Grade 4		
Neuropathy	2 (9)	0 (0)	0 (0)		
Back Pain	0 (0)	1 (4)	0 (0)		
Muscle Cramps	1 (4)	0 (0)	0 (0)		

Abbreviations: *XRCCI* = excision repair cross-complementing-group 1; *XRCCI* = x-ray repair cross-complementing group 1.

^a *XRCCI* (rs11615) and *XRCCI* (rs25487) genotypes were compared with the incidence of toxicities grade 2, which were noted in at least 3 patients; *P*-values are based on an exact Kruskal-Wallis test.