Association Between Polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln Genes and Prognosis of Colorectal Cancer in a Chinese Population

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Abstract

We conducted this study to detect associations between XRCC1 Arg399Gln and XPD Lys751Gln genotypes and survival of colorectal cancer patients treated with 5-FU/oxaliplatin chemotherapy. We included 289 Chinese patients with advanced colorectal cancer, who had received 5-FU/oxaliplatin chemotherapy as first-line treatment from January 2005 to January 2007. All patients were followed up till Nov. 2011. Genotyping for XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms was based upon duplex polymerase-chain-reaction with the PCR-RFLP method. In our study, we found the XRCC1 399 Gln/Gln genotype to confer significantly higher rates of response to chemotherapy when compared to the Arg/Arg genotype [OR (95% CI)= 2.56(1.57-2.55)]. Patients with the XPD 751 Gln/Gln genotype had significantly higher rates of response to chemotherapy [OR (95% CI)= 1.54(0.87-2.65)] and those with the XRCC1 399 Gln/Gln genotype had a longer average survival time and significantly lower risk of death than did those with the Arg/Arg genotype [HR (95% CI)= 0.66(0.36-0.95)]. Similarly, those carrying the XPD 751Gln/Gln genotype had 0.51-fold the risk of death of those with XPD 751Lys/Lys [HR (95% CI) = 0.51(0.33-0.94)]. In conclusion, it is suggested that the XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms should be routinely assessed to determine colorectal patients who are more likely to benefit from 5-FU/oxaliplatin chemotherapy.

Keywords: XRCC1 Arg399Gln - XPD Lys751Gln - polymorphisms - colorectal cancer - chemotherapy - response

Introduction

Colorectal cancer is the third most common cancer diagnosed in the world and the leading cause of cancer death in western industrialized countries (IARC, 2008). Genetic susceptibility to this disease may result from inherited mutations in genes involved in carcinogenesis. Deficit of adequate function of DNA repair gene could accelerate genetic instability and the rate of genetic change, and thus enhance the probability of carcinogenesis (Mohrenweiser and Jones, 1998; Shilds and Harris, 2000). Moreover, these DNA repair genes are reported to have a role in the prognosis of colorectal cancer. XRCC1 is a base excision repair and single strand break repair protein that may play an important role in resistance to variety of DNA damaging agents. Single nucleotide polymorphism of genes involved in the NER pathway affects DNA repair capacity, and therefore, influences the prognosis of malignant diseases (Zhou et al., 2004; Handra-Luca et al., 2007; McWilliams et al., 2008; Shore et al., 2008; Chang et al., 2009).

XRCC1 is a base excision repair and single strand break repair protein that may play an important role in resistance to variety of malignant diseases. Single nucleotide polymorphism of genes involved in the NER pathway affects DNA repair capacity, and therefore, influences the prognosis of malignant diseases (Zhou et al., 2004; Handra-Luca et al., 2007; McWilliams et al., 2008; Shore et al., 2008; Chang et al., 2009). XRCC1 is a base excision repair and single strand break repair protein that may play an important role in resistance to variety of DNA damaging agents. In our previous studies, we found the XRCC1 is related to colorectal cancer susceptibility, and we may hypothesis this type of gene may influence the survival of colorectal cancer (Chang-Claude et al., 2005). A SNP in the XRCC1 gene, consisting of a nucleotide substitution of G to A, designated as XRCC1-01, results in an Arg to Gln amino acid change at codon 399. Although the functional consequences of this polymorphism are unknown, it may affect several protein-protein interactions (Zhao et al., 2012). In vitro, tumor cell lines homozygous for the XRCC1-01 AA genotype are more resistant to a diverse array of anti-cancer and cytotoxic drugs compared with the AG or the GG (least resistant) variants. These include alkylating agents such as busulfan, thiotepa, carboplatin, and cisplatin; DNA/RNA antimetabolites such as fluorouracil; and antimitotics such as vinblastine (Lunn...
Xeroderma pigmentosum group D(XPD), also known as the excision repair cross-complementing group 2(ERCC2), possessed both single- and single-strand DNA-dependent adenosine triphosphate (ATPase) and 5’-3’ DNA helicase activities and is thought to participate in DNA unwinding during NER and transcription (Sung et al., 1993; Hoeijmakers et al., 1996). XPD is an important component of the NER pathway and is capable of reversing ionizing radiation-induced damage and DNA damage by chemotherapy (Parshad et al., 1993; Schaeffer et al., 1994). One common nucleotide polymorphism at codon 751 of XPD results in lysine to glutamine substitution has been proposed to predict responses as well as survival to platinum-based chemotherapy in colorectal cancer risk (Park et al., 2001).

However, there were inconsistency results in the influence of XRCC1 Arg399Gln and XPD Lys751Gln on the survival of several cancers (Chang-Claude et al., 2005; Zhao et al., 2012). Therefore, whether these polymorphisms may influence the susceptibility to 5-FU/oxaliplatin chemotherapy in colorectal cancer is interested. Therefore, we conducted this study to determine the association between the association of XRCC1 Arg399Gln and XPD Lys751Gln genotypes and survival of colorectal cancer patients treated with 5-FU/oxaliplatin chemotherapy.

Materials and Methods

Patients

We included 327 Chinese patients with advanced colorectal cancer, who had received 5-FU/oxaliplatin chemotherapy as first-line treatment from January 2005 to January 2007. Among them, 289 patients were enrolled and analyzed. The remainder were excluded due to dying before blood sampling, unwilling to participate or loss of follow-up. The FOLFOX regimen consisted of a 2-week cycle of oxalipatin (85mg/m²) and leucovorin (LV) (200 mg/m²), before bolus 5-FU (300mg/m²), and continuous infusion of 5-FU (600mg/m²).

The response of treatment were evaluated on the basis of standard response evaluation criteria in Solid Tumors(RECIST) criteria. Patients were subsequently grouped as responders (complete+partial response) or nonresponders (stable+progressive disease). Cases with secondary or recurrent tumors were excluded. All patients were followed up till Nov. 2011. The institutional review board approved this study and informed consent was given by all patients before blood testing for genotyping.

Examination of the XRCC1 and XPD gene polymorphisms

The DNA samples were obtained from stored blood samples using the Qiagen Blood Kit (Qiagen, Chastworth, CA). Genotyping for XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms was based upon duplex polymerase-chain-reaction with the PCR-RFLP method. The primer sequences of XRCC1 Arg399Gln gene were 5’-GAACTCCCTGAAAAGCTAAAGC-3’ and 5’-CTCTAATACGCTTGGGGCT-3’. The primers for the XPD Lys751Gln gene were 5’ GCC CGC TCT GGA TTA TAC G 3’ and 5’ CTA TCA TCT CCT GCC CCC C 3’. Polymerase chain reaction conditions were used as follows: an initial melting step of 5 min at 94°C; 35 cycles of denaturation for 30 s at 94°C; annealing for 30 s at 55°C; extension for 45 s at 72°C, followed by a 5 min final extension at 72°C. We also performed the genotyping of internal positive control samples, use of no template controls, and use of replicates for 10% samples for quality control. These results of the quality control analysis confirmed 100% concordance.

Statistical analysis

Statistical analysis was performed by using SPSS version 16.0 statistical software (SPSS, Chicago, IL, USA). The descriptive data for the major characteristics of study groups were expressed as mean and percent. Pearson’s 2×2 χ²-test (gender) and independent sample t-test(mean age) were used for analysis the differences of several qualitative and quantitative data. The association of polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln with response to chemotherapy in colorectal cancer patients were calculated by odds ratios(OR). The odds ratio was expressed with a corresponding 95% confidence interval (CI). The relative risk [hazard ratio (HR)] and 95% CI were calculated with the Cox regression model for all significant predictors from cancer diagnosis to the endpoint of the study (event). A primary death from colorectal cancer was defined as a failure event, and the survival time was defined as the time between diagnosis and death. The cause of death was defined by specialists based on clinical documents and reports by patients’ family members. If a patient died from a cause other than colorectal cancer, her data was censored at the date of death. Statistical significance was set at P<0.05 and all tests were two-sides.

Results

The clinical features of 289 colorectal cancer patients are summarized in Table 1. The median age at diagnosis

| Characteristics | Responders % | Nonresponders % | P value |
|-----------------|--------------|-----------------|--------|
| Sex             |              |                 |        |
| Male            | 116          | 68              | 64.4   | 0.93 |
| Female          | 67           | 38              | 35.6   | <0.05 |
| Mean age (years)| 51.5±8.7     | 57.5±9.4        |        |
| BMI             |              |                 |        |
| <18.5           | 55           | 33              | 31.5   |        |
| 18.5-23.9       | 59           | 36              | 33.7   |        |
| ≥24             | 68           | 37              | 34.8   | 0.91 |
| UICC TNM stage  |              |                 |        |
| I               | 44           | 27              | 25.3   |        |
| II              | 50           | 29              | 27.6   |        |
| III             | 49           | 27              | 25.7   |        |
| IV              | 40           | 23              | 21.4   | 0.993 |
| Distant metastasis |          |                 |        |
| M-              | 140          | 79              | 74.3   |        |
| M+              | 43           | 27              | 25.7   | 0.689 |
| Localisation    |              |                 |        |
| Rectum          | 95           | 50              | 47.3   |        |
| Colon           | 88           | 56              | 52.7   | 0.44 |
Table 2. Genotype Characteristics of the Two SNPs

| Single nucleotide | Major/minor Alleles | Minor Allele | HWE (P value) | Genotypes | n=183 | n=106 |
|-------------------|---------------------|--------------|--------------|-----------|-------|-------|
| Gln/Gln           | 56                  | 33           | 0.56(0.35-2.85) | Arg/Arg   | 95    | 51.7 |
|                   |                     |              |              | Arg/Gln   | 56    | 30.6 |
|                   |                     |              |              | Gln/Gln   | 32    | 17.7 |
|                   |                     |              |              | Gln allele| 60    | 33   |
| Lys/Lys           | 191                 | 93           | 0.85(0.51-1.23) | Arg/Arg   | 95    | 51.7 |
|                   |                     |              |              | Arg/Gln   | 88    | 30.6 |
|                   |                     |              |              | Gln/Gln   | 51    | 17.7 |
|                   |                     |              |              | Gln allele| 191   | 3335.6 |
| Lys/Lys           | 138                 | 67           | 0.66(0.36-0.95) | XPD Lys751Gln (rs13181) | 751Lys/Lys | 56    | 30.7 |
|                   |                     |              |              | Lys/Gln   | 125   | 43.3 |
|                   |                     |              |              | Gln/Gln   | 26    | 9.1  |
|                   |                     |              |              | Gln allele| 89    | 30.7 |

1 Adjusted for age, sex, BMI, UICC TNM stage, distant metastasis and localization

Table 3. Distribution of XPD and XRCC1 in Responders and Non-responders to Chemotherapy for Colorectal Cancer

| Single nucleotide | Major/minor Alleles | Minor Allele | HWE (P value) | Genotypes | n=183 | n=106 |
|-------------------|---------------------|--------------|--------------|-----------|-------|-------|
| Gln/Gln           | 32                  | 12           | 1.84(1.07-3.98) | Arg/Arg   | 95    | 51.7 |
|                   |                     |              |              | Arg/Gln   | 98    | 30.6 |
|                   |                     |              |              | Gln/Gln   | 52    | 17.7 |
|                   |                     |              |              | Gln allele| 191   | 3335.6 |
| Lys/Lys           | 87                  | 52           | 2.67(1.21-8.05) | XPD Lys751Gln (rs13181) | 751Lys/Lys | 56    | 30.7 |
|                   |                     |              |              | Lys/Gln   | 79    | 43.3 |
|                   |                     |              |              | Gln/Gln   | 17    | 9.1  |
|                   |                     |              |              | Gln allele| 56    | 30.7 |

1 Adjusted for age, sex, BMI, UICC TNM stage, distant metastasis and localization

Table 4. Hazard Ratios for Overall Survival in Colorectal Cancer Patients with Chemotherapy

| Genotypes | N | % | Median Survival time (months) | HR (95% CI) |
|-----------|---|---|------------------------------|-------------|
| XRCC1 Arg399Gln (rs25487) | 183 | 51.7 | 33.3 | 0.56(0.35-2.85) | 0.51(0.33-0.94) |
| Arg/Arg   | 95 | 51.7 | 33.3 | 0.85(0.51-1.23) | 0.51(0.33-0.94) |
| Arg/Gln   | 88 | 30.6 | 33.6 | 1.03(0.56-1.71) | 0.51(0.33-0.94) |
| Gln/Gln   | 51 | 17.7 | 37.7 | 1.31(0.77-2.06) | 0.51(0.33-0.94) |
| Gln allele| 191| 3335.6 | 33.3 | 1.66(0.36-0.95) | 0.51(0.33-0.94) |
| XPD Lys751Gln (rs13181) | 751Lys/Lys | 56 | 30.7 | 33.3 | 0.66(0.36-0.95) | 0.51(0.33-0.94) |
| Lys/Gln   | 125| 43.3 | 34.9 | 1.91(0.66-1.87) | 0.51(0.33-0.94) |
| Gln/Gln   | 26 | 9.1  | 36.1 | 0.51(0.33-0.94) | 0.51(0.33-0.94) |
| Gln allele| 89 | 30.7 | 34.2 | 0.56(0.35-2.85) | 0.51(0.33-0.94) |

Discussion

Among all patients, the median survival time was 34.2 months. Patients with XRCC1 399 Gln/Gln genotype had a longer average survival time and significantly lower risk of death than those with Arg/Arg genotype [HR (95% CI) = 0.66(0.36-0.95)] (Table 4). Similarly, those carrying XPD 751Gln/Gln genotype had 0.51-fold the risk of death of those with XPD 751Lys/Lys [HR (95% CI) = 0.51(0.33-0.94)] (Table 4).

Table 4. Hazard Ratios for Overall Survival in Colorectal Cancer Patients with Chemotherapy

1 Adjusted for age, sex, BMI, UICC TNM stage, Distant metastasis and Localisation

was 51.5±8.7 years. Among 289 patients, 183 patients were responders and 106 were nonresponders to chemotherapy. Among the responders, 71 showed a complete response and 112 showed a partial response. Patients had higher age and lower response to chemotherapy (P<0.05).

The allele and genotype distribution of polymorphisms in XRCC1 Arg399Gln and XPD Lys751Gln were shown in table 2. The minor allele frequencies among selected cancer. These inconsistency results might be due to source of patients, disease stages, sample size and by chance. Further multicenter studies are warranted to establish the impact of XRCC1 and XPD genotypes on chemotherapy.

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Discussion

To our best of our knowledge, no studies have investigated the role of DNA-repair gene, XRCC1 and XPD, on the response to chemotherapy among patients suffering colorectal cancer. Our results showed a significant association between XRCC1 399Gln/Gln and XPD 751Gln/Gln genotype and response to chemotherapy among colorectal cancer patients, moreover, the two genotypes could influence the survival of colorectal cancer.

Since this is the first study on the association between XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms and the response to chemotherapy. Previous evidences showed the XRCC1 Arg399Gln and XPD Lys751Gln are involved in response to chemotherapy in various cancers, such as breast cancer, thyroid carcinoma and lung cancer (Fard-Esfahani et al., 2011; Raabe et al., 2012). However, there are few studies in Chinese colorectal cancer patients on these two genes. Only several studies conducted in China investigation the association of XRCC1 with chemotherapy response and survival of colorectal cancer, but the results are conflicting (Grimminger et al., 2010; Lamas et al., 2012; Lv et al., 2012). A study conducted in China reported XRCC1 Arg399Gln polymorphisms is associated with the response to oxaliplatin-based chemotherapy and time to progression in advanced colorectal cancer in Chinese population, and patients with G/G genotype showed enhanced respond to chemotherapy compared to those with G/A and A/A genotypes. Individuals with the G/G genotype had a TTP of 10.0 (8.88-11.12) months, those with the G/A+A/A genotype had an TTP of 5.0 (4.26-5.74) months Lv et al. (2012). While another study reported patients with A/A had better respond to chemotherapy, and had a higher survival time than those with G/A and G/G genotypes. Our study finds a significant association of XRCC1 399Gln/Gln genotype with increased survival and higher response to chemotherapy among patients suffering colorectal cancer. These inconsistency results might be due to source of patients, disease stages, sample size and by chance. Further multicenter studies are warranted to establish the impact of XRCC1 and XPD genotypes on chemotherapy.

There are few studies reporting the association between XPD genotypes and response to chemotherapy among colorectal cancer patients. XPD protein, encoded by XPD gene, plays a role in NER pathway. During the NER, XPD participates in the opening of the DNA helix to allow the excision of the DNA fragment containing the damaged base (Manuguerra et al., 2006). 751 (Lys to Gln) were the main polymorphism that induce amino acid changes in the proteins (Shen et al., 1998). Previous
experimental studies showed the XPD codon Lys751Gln could modify the DNA repair ability in the NER capacity, and XPD 751Gln alleles had lower NER capacity than the wide-type genotypes (Rzeszowska-Wolny et al., 2005). In previous epidemiologic studies, only three western studies reported the XPD was associated with the progression-free survival. A study conducted in Spain reported XPD 751Gln/Gln was significantly associated with a favorable survival of colorectal cancer when compared with XPD 751Lys/Lys genotype (Lamas et al., 2011). While another study in Taiwan reported an reverse results of XPD 751Gln for colorectal survival (Lai et al., 2009). Our study showed modern increased survival in XPD 751Gln/Gln carriers, which is obvious because XPD 751Gln/Gln have reduced the activity and thus may have decreased DNA repair capabilities. The chemotherapy for colorectal cancer is to induce the DNA damage of cancer cells, the low activity of XRCC1 and XPD polymorphisms would strengthen susceptibility to chemotherapy.

In summary, we found polymorphisms of XRCC1 399Gln/Gln and XPD 751Gln/Gln in Chinese population might be greatly strengthen the susceptibility to 5-FU/oxaliplatin chemotherapy among Chinese population, it is suggested that the XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms should be routine detected to colorectal patients who are more likely benefit from 5-FU/oxaliplatin chemotherapy.

References

Chang-Claude J, Popanda O, Tan XL, et al. (2005). Association between polymorphisms in the DNA repair genes, XRCC1, APE1, and XPD and acute side effects of radiotherapy in breast cancer patients. Clin Cancer Res, 11, 4802-9.

Chang PM, Tzeng CH, Chen PM, et al. (2009). ERCC1 codon 118 C>T polymorphism associated with ERCC1 expression and clinical outcome to FOLFOX-4 treatment in Asian patients with metastatic colorectal carcinoma. Cancer Sci, 100, 278-83.

Fard-Esfahani P, Fard-Esfahani A, Fayaz S (2011). Association of Arg194Trp, Arg280His and Arg399Gln polymorphisms in X-ray repair cross-complementing group 1 gene and risk of differentiated thyroid carcinoma in Iran. Iran Biomed J, 15, 73-8.

Grimminger PP, Brabender J, Warnecke-Eberz U, et al. (2010). VallabhshettiXRCC1 gene polymorphism for prediction of response and prognosis in the multimodality therapy of patients with locally advanced rectal cancer. J Surg Res, 164, 616-1.

Handra-Luca A, Hernandez J, Mountzios G, et al. (2007). Excision repair cross complementation group1 immunohistochemical expression predicts objective response and cancer-specific survival in patients treated by cisplatin-based induction chemotherapy for locally advanced head and neck squamous cell carcinoma. Clin Cancer Res, 13, 3855-9.

Hoeijmakers JH, Egly JM, Vermeulen W (1996). TFIH: a key component in multiple DNA transaction. Curr Opin Gene Dev, 6, 26-33.

International Agency for Research on Cancer (2008). Colorectal Cancer Incidence and Mortality Worldwide in 2008. http://globocan.iarc.fr.

Lai JI, Tzeng CH, Chen PM, et al. (2009). Very low prevalence of XPD K751Q polymorphism and its association with XPD expression and outcomes of FOLFOX-4 treatment in Asian patients with colorectal carcinoma. Cancer Sci, 100, 1261-6.

Lamas MJ, Duran G, Balboa E, et al. (2011). Use of a comprehensive panel of biomarkers to predict response to a fluorouracil-oxaliplatin regimen in patients with metastatic colorectal cancer. Pharmacogenomics, 12, 433-42.

Lamas MJ, Duran G, Gomez A, et al. (2012). D X-ray cross-complementing group 1 and thymidylate synthase polymorphisms might predict response to chemoradiotherapy in rectal cancer patients. Int J Radiat Oncol Biol Phys, 82, 138-44.

Lunn RM, Langlois RG, Hsieh LL, et al. (1999). XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res, 59, 2557-61.

Lv H, Li Q, Qiu W, et al. (2012). Genetic Polymorphism of XRCC1 Correlated with Response to Oxaliplatin-Based Chemotherapy in Advanced Colorectal Cancer. Pathol Oncol Res, 18, 1009-14.

Manuguerra M, Saletta F, Karagas MR, et al. (2006). XRCC3 and XPD/ERCC2 single nucleotide polymorphisms and the risk of cancer: a HuGE review. Am J Epidemiol, 164, 297-302.

McWilliams RR, Banlet WR, Cunningham JM, et al. (2008). Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res, 68, 4928-35.

Mohrenweiser HW, Jones IM (1998). Variation in DNA repair is a factor in cancer susceptibility: a paradigm for the promises and perils of individual and population risk estimation? Mutat Res, 400, 15-24.

Park DJ, Stoehmacher J, Zhang W, et al. (2001). Xeroderma pigmentosum group D gene polymorphism predicts clinical outcome to platinum-based chemotherapy in patients with advanced colorectal cancer. Cancer Res, 61, 8654-9.

Parshad R, Tarone RE, Price FM, et al. (1993). Cytogenetic evidence for differences in DNA incision activity in xeroderma pigmentosum group A, C and D cells after X-irradiation during G2 phase. Mutat Res, 294, 149-55.

Raabe A, Derda K, Reuther S, et al. (2012). Association of single nucleotide polymorphisms in the genes ATM, GSTP1, SOD2, TGFBI, XPD and XRCC1 with risk of severe erythema after breast conserving radiotherapy. Radiat Oncol, 7, 65.

Raymond E, Faivre S, Woynarowski JM, Chaney SG (1998). Oxaliplatin: mechanism of action and antineoplastic activity. Semin Oncol, 25, 4-12.

Rzeszowska-Wolny J, Polanska J, Pietrowska M, et al. (2005). Influence of polymorphisms in DNA repair genes XPD, XRCC1 and MGMT on DNA damage induced by gamma radiation and its repair in lymphocytes in vitro. Radiat Res, 164, 132-40.

Saldivar JS, Wu X, Follen M, Gershenson D (2007). Nucleotide excision repair pathway review I: implications in ovarian cancer and platinum sensitivity. Gynecol Oncol, 107, S56-71.

Schaeffer L, Moncollin V, Roy R, et al. (1994). The ERCC2/DNA repair protein is associated with the class II BTPF2/TFIIH transcription factor. EMBO J, 13, 2388-92.

Shen MR, Jones IM, Mohrenweiser H (1998). Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer research, 58, 604-8.

Shields PG, Harris CC (2000). Cancer risk and low-penetration susceptibility genotypes in gene-environment interactions. J Clin Oncol, 18, 2309-15.

Shore RE, Zeleniuch-Jacquotte A, Currie D, et al. (2008). Polymorphisms in XPC and ERCC2 genes, smoking and breast cancer risk. Int J Cancer, 122, 2101-5.

Sung P, Bailly V, Weber C, et al. (1993). Human xeroderma pigmentosum group D gene encodes a DNA helicase. Nature, 365, 852-5.

Zhao Y, Deng X, Wang Z, et al. (2012). Genetic polymorphisms of DNA repair genes XRCC1 and XRCC3 and risk of colorectal cancer in Chinese population. Asian Pac J Cancer Prev, 13, 665-9.

Zhou W, Gurubhagavatula S, Liu G et al. (2004). Excision repair crosscomplementation group 1 polymorphism predicts overall survival in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. Clin Cancer Res, 10, 4939-43.