RESEARCH ARTICLE

Prediction Value of XRCC 1 Gene Polymorphism on the Survival of Ovarian Cancer Treated by Adjuvant Chemotherapy

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Abstract

Objective: We conducted a prospective study to test the association between three amino acid substitution polymorphic variants of DNA repair genes, XRCC1 (Arg194Trp), XRCC1(Arg280His) and XRCC1 (Arg399Gln), and clinical outcome of ovarian cancer patients undergoing adjuvant chemotherapy. Methods: 195 patients with primary advanced ovarian cancer and treated by adjuvant chemotherapy were included in our study. All were followed-up from Jan. 2007 to Jan. 2012. Genotyping of XRCC1 polymorphisms was conducted by TaqMan Gene Expression assays. Results: The XRCC1 194 Trp/Trp genotype conferred a significant risk of death from ovarian cancer when compared with Arg/Arg (HR=1.56, 95%CI=1.04-3.15). Similarly, those carrying the XRCC1 399 Gln/Gln genotype had a increased risk of death as compared to the XRCC1 399Arg/Arg genotype with an HR (95% CI) of 1.98 (1.09-3.93). Conclusion: This study is the first to provide evidence that XRCC1 gene polymorphisms would well be useful as surrogate markers of clinical outcome in ovarian cancer cases undergoing adjuvant chemotherapy.

Keywords: Ovarian cancer - XRCC1 - adjuvant chemotherapy - polymorphism

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Introduction

Ovarian cancer is the leading cause of death from gynaecologic malignancy. The vast majority of malignant ovarian cancers are of epithelial origin and can be classified into four major subtypes: serous, mucinous, endometrioid, and clear cell. More than 50% of the ovarian cancer patients are diagnosed at an advanced stage (Hogberg et al., 2001). Several regimens of combination chemotherapeutic therapy have been introduced to treat patients with advanced ovarian cancer (Hogberg et al., 2001). Currently, the initial surgery followed by adjuvant chemotherapy is a main methods for ovarian cancer patients (Williams et al., 1989; Harries et al., 2001; Piccart et al., 2001).

As we know, the chemotherapeutic drugs cancer damage DNA directly, through intercalation and also by lipid peroxidation and the formation of by-products, such as reactive oxygen species (La et al., 1997; Weijl et al., 1997). The in vitro and in vivo studies have shown associations between alteration in DNA repair and cell cycle control genes and/or proteins and sensitivity to a broad range of drugs and patient survival (Allan et al., 2004; Zhou et al., 2004; Simon et al., 2005). The single nucleotide polymorphisms (SNPs) in gene involved in DNA repair and cell cycle control can affect repair efficiency, increase cancer risk and significantly alter patient responses to cancer treatments (Allan et al., 2004; Price et al., 2004; Zhou et al., 2004; Zhou et al., 2004). 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. The polymorphisms of three SNPs, resulting in amino acid substitutions, were detected at codons 194 (Arg-Trp), 280 (Arg-His) and 399 (Arg-Gln). Most studies report an increased risk of death from ovarian cancer among patients with 194Trp allele (Cui et al., 2012). The 399 polymorphism was reported to be associated with the prognosis of a number of cancers, although results have been inconsistent (Liang et al., 2010; Liu et al., 2011; Cui et al., 2012; Liao et al., 2012). Few studies have investigated the association between the XRCC1 280His allele and risk of death from cancers.

Therefore, in this present study, we conducted a prospective study to test the association between three amino acid substitution variants of DNA repair genes, XRCC1 (Arg194Trp), XRCC1(Arg280His) and XRCC1 (Arg399Gln) polymorphisms and the clinical outcome ovarian cancer patients with adjuvant chemotherapy.

Materials and Methods

Patients

Patients included in our study had primary advanced ovarian cancer and treated by adjuvant chemotherapy. A total of 210 eligible cases were included between Jan. 2005 to Jan 2007. Among them, 195 patients were interviewed
Table 1. Characteristics of Included Cases in Our Studies

| Variables                  | Cases N=195 | %   |
|----------------------------|-------------|-----|
| Median age(range), years   | 46.5(25.6-72.3) | 100 |
| <40                        | 30          | 15.4|
| 40-60                      | 113         | 57.9|
| >60                        | 52          | 26.7|
| Surgical stage             |             |     |
| I                          | 16          | 8.2 |
| II                         | 21          | 10.8|
| III                        | 139         | 71.3|
| IV                         | 19          | 9.7 |
| Optimal debulking operation as primary operation |  | |
| No                         | 62          | 31.8|
| Yes                        | 133         | 68.2|
| Histological subtype       |             |     |
| Serous adenocarcinoma      | 109         | 55.9|
| Endometrioid adenocarcinoma| 23          | 11.8|
| Clear cell carcinoma       | 34          | 17.4|
| Mucinous adenocarcinoma    | 12          | 6.2 |
| Other adenocarcinomas      | 17          | 8.7 |
| Menopausal status          |             |     |
| Pre                        | 63          | 32.3|
| Post                       | 132         | 67.7|

with a participation rate of 92.9%. After patients provided informed consent, every patient required to provide 5 ml bloods. All the patients were followed every 2 months until death or the end of follow-up. Survival time was calculated from the date of diagnosis to the date of death or the end of follow-up. All the 195 patients were followed-up from Jan. 2007 to Jan. 2012.

Adjuvant chemotherapy

The treatment program consisted of bleomycin 15 mg/day on days 1 to 3 as an intravenous (IV) infusion in 1000 ml normal saline for 24 h. Etoposide was given at a dose of 100 mg/m²/day IV on day 1 to 3 for 2 h and cisplatin 20 mg/m²/day IV on days 1 to 5 for 1 h. The cycles were repeated every 3 weeks.

Genotyping

Genotyping of 3 SNPs of XRCC1 was carried out by using the TaqMan allelic discrimination assay on a Sequence Detection System ABI 700 (Applied Biosystems). The XRCC1 polymorphisms (XRCC1 Arg194Trp, XRCC1 Arg280His and XRCC1 Arg399Gln) were determined in a 12 μl reactions containing 1x MasterMix, 200 nM of each probe, 900 nM primers, and 50–100 ng of genomic DNA. Cycling conditions were as follows: 50°C for 2 min, 95°C for 10 min, and 45 cycles of 95°C for 15 s and 60°C for 1 min. Primers and probes are described in previous studies (Butkiewicz et al., 2011). We used replicates for 10% samples for quality control.

Statistical analysis

Statistical analysis was performed by using the STATA statistical package (version 10.0, STATA, College Station, TX). The descriptive data for the major characteristics of study groups are expressed as mean and percent. Pearson’s 2x2 χ²-test (gender) and independent sample t-test (mean age) were used for analysis the differences of several qualitative and quantitative data. The primary predictors associated with response to chemotherapy, and Cox’s proportional hazard regression model was applied to identify independent predictors associated with response to chemotherapy, and Cox’s proportional hazard regression model was taken for the survival analysis. The analysis was adjusted for age, surgical stage, menopausal status and histological subtype. The hazard ratio (HR) and 95% confidence interval (CI) were also estimated. A cut-off P value of 0.05 was adopted for all the statistical analysis. Statistical significance was defined as a 2-sided P-value of less than 0.05.

Results

All the 195 patients were followed-up until Jan, 2012. The median follow-up time was 30.1 months, and 114 patients died during the five years follow-up. The clinical characteristics of cases showed in Table 1. The median age of included cases was 46.5(25.6-72.3) years, and about 58% of the patients were at the range of 40-60 years old. More than 50% of patients received optimal debulking operation as primary operation. 158 patients (81%) were at the stage of III and IV, and 109 patients (55.9%) were serous adenocarcinoma. 132 patients (67.7) were post menopausal status when diagnosis. The higher stage of ovarian cancer was likely to increase the risk of death from ovarian cancer [HR(95% CI)=2.21(1.23-4.57) for stage III and HR(95% CI)=2.68(0.53-6.13) for stage IV, data not shown].

The frequencies of XRCC1 Arg194Trp, Arg280His and Arg399Gln genotypes in ovarian cancer cases were showed in Table 2. Our study showed XRCC1 Arg194Trp/Trp genotype had a significant risk of death from ovarian cancer when compared with individuals with Arg/Arg, and with a significant increased death risk (HR=1.56, 95%CI=1.04-3.15) (Figure 1). Similarly, those carrying
However, both of them did not found a significant association of XRCC1 Arg194Trp and XRCC1Arg399Gln gene polymorphisms with survival of ovarian cancer. Two studies conducted in Korea and Russian reported the association of XRCC1-194 and 399 with the risk in non-small-cell lung cancer (NSCLC) (Kiyohara et al., 2006), colorectal cancer (Stern et al., 2006), gastric cancer (Huang et al., 2005) and prostate cancer (Hirata et al., 2007). Only two recent studies have reported on the pharmacogenetic role of XRCC1-399 and -194 polymorphisms in ovarian cancer patients (Kim et al., 2009; Khrunin et al., 2010). Our results contradict the current understanding of XRCC1 involvement in platinum compound-based chemotherapy. Since people in different parts of China have different living standards and lifestyles, the apparent inconsistency of these reports may be due to differences in environment factors. Since we did not collect the lifestyle and living standard information on these patients, we did not explore the association between these factors and XRCC1 polymorphisms. Further studies are warranted to explore their association.

In conclusion, this study is the first time to reported the XRCC1 gene polymorphisms would well be useful as a surrogate marker of clinical outcome in ovarian cancer with adjuvant chemotherapy. Further, prospective studies incorporating larger numbers of patients would be necessary to validate its predicted value.

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