African Journal of Pharmacy and Pharmacology Vol. 6(33), pp. 2472-2476, 5 September, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP12.603
ISSN 1996-0816 © 2012 Academic Journals

Full Length Research Paper

Study on the DNA repair gene ERCC1 and XPD polymorphism in prediction of survival of glioma patients with chemotherapy

Song Chang-xin[1*], Wang Ting[1] and Chen Da-qing[2]

[1]Department of Computer, Qinghai Normal University, 810008, Xining, China.
[2]The Affiliated Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Accepted 13 July, 2012

Tumors of the central nervous system (CNS) account for about 2% of all the cancers, and gliomas are the most common tumors of CNS. Although there is a great improvement of the diagnosis and treatment, the prognosis of glioma is poor and this tumor remains incurable. We conducted a perspective case cohort study to examine the role of genetic polymorphisms in Excision repair cross-complementing group 1 (ERCC1) and xeroderma pigmentosum group D (XPD) on the prognosis of glioma in Chinese population. Three hundred and fifty patients that underwent procarbazine, lomustine, and vincristine (PCV) chemotherapy were selected between November 2007 and November 2011, and all of them were followed-up till April 2012. The genotyping of ERCC1 118C/T (rs3212986), ERCC1 8092C/A(rs11615), XPD Lys751Gln(rs13181) and XPD Asp312Asn(rs1799793) was performed by TaqMan assays. The Cox's regression analysis showed individuals carrying ERCC1 118 T/T genotype with 0.56 fold risk of death from glioma than ERCC1 118 T/T genotype (HR=0.56, 95%CI=0.33-0.87). Meanwhile, XPD 751Gln/Gln had a moderate lower hazard ratio (HR) of glioma in comparison to XPD Lys/Lys carriers (HR=0.53, 95%CI=0.37-0.94). In conclusion, our present data indicated that polymorphisms in ERCC1 118C/T (rs3212986) and XPD Lys751Gln(rs13181) have a role in the prognosis of glioma.

Key words: DNA repaired gene, glioma, chemotherapy, prognosis.

INTRODUCTION

Tumors of the central nervous system (CNS) account for about 2% of all the cancers, and gliomas are the most common tumors of CNS. Although there is great improvement of the diagnosis and treatment, the prognosis of glioma is poor and this tumor remains incurable. The etiology for this tumor is poorly understood. In addition to hereditary syndromes, the only established risk factor was ionizing radiation (Ron et al., 1988; Sadetzki et al., 2005). However, since both the exposure of inherited disorders and irradiation are rare, only a minority of brain neoplasms are found. Recently, the variability of DNA repair function caused by the polymorphisms in related genes plays a role in the risk of glioma. Base excision (BER) pathway is a main system of DNA repair. There were two main genes, excision repair cross-complementing rodent repair deficiency complementation group 1(ERCC1) gene and xeroderma pigmentosum group D (XPD), involved in the BER pathway. The polymorphisms in the two genes are responsible for influencing the DNA repair function and amending small lesions, such as single-strand breaks (SSBs), non-bulky adducts, oxidative damage, alkylation and methylation.

The DNA repaired mechanisms are hypothesized to be play an important role in the sensitivity to chemotherapy and radiotherapy among patients with non-small cell lung cancer, breast cancer, head and neck squamous cell

*Corresponding author. E-mail: chendaqing5456@163.com; songcx321@163.com.

cancer as well as pancreatic cancer (Giovannetti et al., 2011; Azad et al., 2012; Zhang et al., 2011; Rybárová et al., 2011; Xu et al., 2011). However, their role in brain carcinogenesis glioma has not been established. Only several studies evaluated the possible association of ERCC1 and XPD SNPs and the risk of developing glioma, and no studies researched on the association between the gene polymorphisms and cancer prognosis. In the present analysis, we conducted a perspective case cohort study to examine the role of genetic polymorphisms in ERCC1 and XPD on the prognosis of glioma in Chinese population.

METHODOLOGY

A total of 398 cases with primary brain tumors were collected in our study. All were Chinese cases with newly diagnosed primary glioma between November 2007 and November 2011. All the cases were identified from oncology, neuropathology and neurosurgery departments of our hospital. A total of 398 eligible cases were collected and 350 patients agreed to participate, with the participation rate of 87.9%. Informed consent was obtained from patients and the study was approved by the ethnical review board of our hospital.

Information on medical history, occupational exposure, smoking habits and family history of cancer were obtained from face to face interviews by nurses or doctors. All the patients were asked to provide 5 ml blood sampling to genotyping and donate a blood sample. After surgery, patients with glioma underwent PCV chemotherapy [procarbazine, methyl-1-(2-chloroethyl)-1-nitrosourea (CCNU), and vincristine] every 6 weeks (42-day cycles) for two to five cycles).

All the 350 patients were followed-up till April 2012. During the follow-up, 23 patients were lost to follow-up due to immigrant, psychological factor or cognitive disability. A total of 327 patients were followed-up.

Genotyping

The genomic DNA was extracted from peripheral blood samples using the Qiagen Blood Kit (Qiagen, Chatsworth, CA). Genotyping of ERCC1 118C/T(rs3212986), ERCC1 8092C/A(rs11615), XPD Lys751Gln(rs13181) and XPD Asp312Asn(rs1799793) was conducted by TaqMan assays using the ABI Prism 7911HT Sequence Detection System (Applied Biosystems, Foster City, CA). The primers of the rs3212986 were 5′-AGACTACACAGGCTGCTGCTGCTGCT-3′ and 5′-CTTCCGCT TCTTGTCCCGGCCTGTG-3′; primers of rs11615 were 5′-AATCCCGTACTGAAGTTCGTGCGCAA-3′ and 5′-GTGCCCT GGGAATTTGGCGACGTAA-3′; primers of rs13181 were 5’-CTGCTGAGCAATCTGCTCTATCCTCT-3′ and 5′-CAGCGTCTCC TCTGATTCTAGCTGC-3′; while primers of rs1799793 were 5′-CCCACCTGGCCAACCCCGTGCTGCCC-3′ and 5′-ACGAAGTGCTGCAGGGTGAGCCCCG-3′. The condition of reaction were as follows: initial denaturation for 10 min at 95°C, followed by 40 cycles of 15 s at 92°C and 60 s at 60°C. Genotyping was done by laboratory personnel blinded to the case status. Moreover, 10% of the cases were used for quality control in our study, and the reproducibility was 100%.

Statistical analysis

Stata 8.0 (StataCorp, College Station, USA) was used to perform statistical analyses. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were shown as frequencies and percentages. The outcome for glioma was overall survival, which was estimated using the Kaplan-Meir method. A univariate Cox’s regression analysis was used to assess the association of polymorphisms in ERCC1 118C/T(rs3212986), ERCC1 8092C/A(rs11615), XPD Lys751Gln(rs13181) and XPD Asp312Asn(rs1799793) with survival of glioma. The relative risk [hazard ratio (HR)] and 95% CI were calculated from the Cox regression model for all significant predictors from cancer diagnosis to the endpoint of the study (event). All statistical tests were two sided and differences were taken as significant when the P value was less than 0.05.

RESULTS

During the follow-up, a total of 172 patients (49.1%) died. The median survival of patients was 28.1 ± 6.3 months (2 months to 52 months). The mean age of the enrolled cases was 51.9 ± 8.3 years (Table 1). The older age of cases had higher risk of death from glioma, with the HR (95% CI) of 1.20 (0.85 - 1.66). Female glioma cases showed longer survival than males. The longer survival was found in glioma with lower grade glioma, and the HR (95% CI) was 1.57(1.03-2.23).

Compared with ERCC1 118T/T genotype, a significant difference in the median survival time was found among patients carrying C/C and C/T genotype (25.7 ± 8.5 and 29.3 ± 7.6 months vs. 37.4 ± 4.7 months, respectively) (Table 2). Individuals with XPD 751 Gln/ Gln genotypes had significantly different survival time than patients carrying Lys/Lys and Lys/Gln genotypes (24.5 ± 6.9 and 28.8 ± 8.3 months vs. 38.9±7.4 months) (Figure 1). The Cox’s regression analysis indicated that individuals carrying ERCC1 118T/T genotype showed 0.56 fold risk of death from glioma than ERCC1 118 C/C genotype (HR=0.56, 95%CI=0.33-0.87). Meanwhile, XPD 751Gln/Gln had a moderate lower HR of glioma in comparison to XPD Lys/Lys carriers (HR=0.53, 95%CI=0.37-0.94) (Figure 2). However, ERCC1 8092C/A and XPD Asp312Asn did not show significant association with survival of glioma.

DISCUSSION

The present study investigated the association of ERCC1 118C/T(rs3212986), ERCC1 8092C/A(rs11615), XPD Lys751Gln(rs13181) and XPD Asp312Asn(rs1799793) with susceptibility to glioma. Our results showed a significant decreased risk of death from glioma among individuals carrying ERCC1 118C/C and XPD 751Gln/Gln genotypes. However, we did not find ERCC1 8092C/A and XPD Asp312Asn to be related to prognosis of glioma. Meanwhile, there are limited report on the role of ERCC1 118C/T and XPD Lys751Gln polymorphisms on the survival of cancer patients. The DNA repair systems are critical for repairing DNA damage induced by carcinogens. Moreover, they also play an important role in repairing the

Table 1. Kaplan-Meier analysis for overall rate of patients with glioma by characteristics.

Variable	Cases (%) (N = 350)	Mean survival time (months)	HR (95% CI)	P value
Age	51.9 ± 8.3			
<30	47 (13.8)	32.6 ± 4.7	-	-
30-50	115 (33.7)	29.5 ± 6.6	1.11 (0.74 - 1.65)	0.24
>50	179 (52.5)	26.1 ± 7.2	1.20 (0.85 - 1.66)	0.13
Sex				
Male	226 (66.5)	27.6 ± 6.8	-	-
Female	114 (33.5)	31.6 ± 7.2	0.94 (0.51 - 1.32)	0.55
Histological grade				
High grade	203 (59.6)	24.6 ± 7.4	-	-
Low grade	137 (40.4)	36.5 ± 6.6	1.57 (1.03 - 2.23)	<0.05

Table 2. The survival of glioma by polymorphisms in ERCC1 and XPD genes.

Genotype	Case (%) (N = 350)	Mean survival time (months)	HR (95% CI)[1]	P value
ERCC1 118C/T (rs3212986)				
C/C	146 (41.6)	25.7 ± 8.5	-	-
T/C	128 (36.7)	29.3 ± 7.6	0.87 (0.67 - 1.23)	0.11
T/T	76 (21.7)	37.4 ± 4.7	0.56 (0.33 - 0.87)	<0.05
ERCC1 8092C/A (rs11615)				
C/C	174 (49.7)	24.7 ± 7.1	-	-
A/C	128 (36.5)	27.6 ± 7.0	0.97 (0.74 - 1.36)	0.54
A/A	48 (13.8)	32.3 ± 5.7	0.87 (0.43 - 1.23)	0.22
XPD Lys751Gln (rs13181)				
Lys/Lys	128 (36.7)	24.5 ± 6.9	-	-
Lys/Gln	170 (48.6)	28.8 ± 8.3	0.75 (0.94 -1.63)	0.31
Gln/ Gln	51 (14.7)	38.9 ± 7.4	0.53 (0.37 - 0.94)	<0.05
XPD Asp312Asn (rs1799793)				
Asp/Asp	160 (45.7)	26.7 ± 7.3	-	-
Asp/Asn	147 (42.1)	29.8 ± 8.2	0.83(0.52 - 1.31)	0.23
Asn/ Asn	43 (12.2)	35.4 ± 6.9	0.76(0.44 - 1.15)	0.14

[1]Adjusted for age, sex and histological grade.

cross-linking and oxidative damage caused by chemotherapy drugs (Altaha et al., 2004). Therefore, the impaired DNA repair capacity may not only increase carcinogenesis and lead to more biologically aggressive tumors and decrease survival, but also contribute to the persistence of functional chemotherapy drug-DNA adducts that confer anti-tumor activity and impart more favorable prognoses.

The ERCC1 and XPD are two major repair genes involved in base excision repair (BER) of the DNA repair system. Mutations and polymorphisms in DNA repair genes are associated with variations in the repair efficiency of DNA damage, and this repair deficit may increase the risk of cancer, birth defects and a reduced life span (Ronen and Glickman, 2001). These variations in the evolutionarily conserved amino acid residues in the protein-protein interface could alter the function of protein and increase the cancer risk (Chacko et al., 2005). The role of ERCC1 and XPD polymorphisms has been reported to be associated with function of chemotherapy of several cancers, including non-small cell lung cancer, breast cancer, head and neck squamous cell cancer as well as pancreatic cancer (Giovannetti et al., 2011; Azad et al., 2012; Zhang et al., 2011; Rybárová et al., 2011; Xu

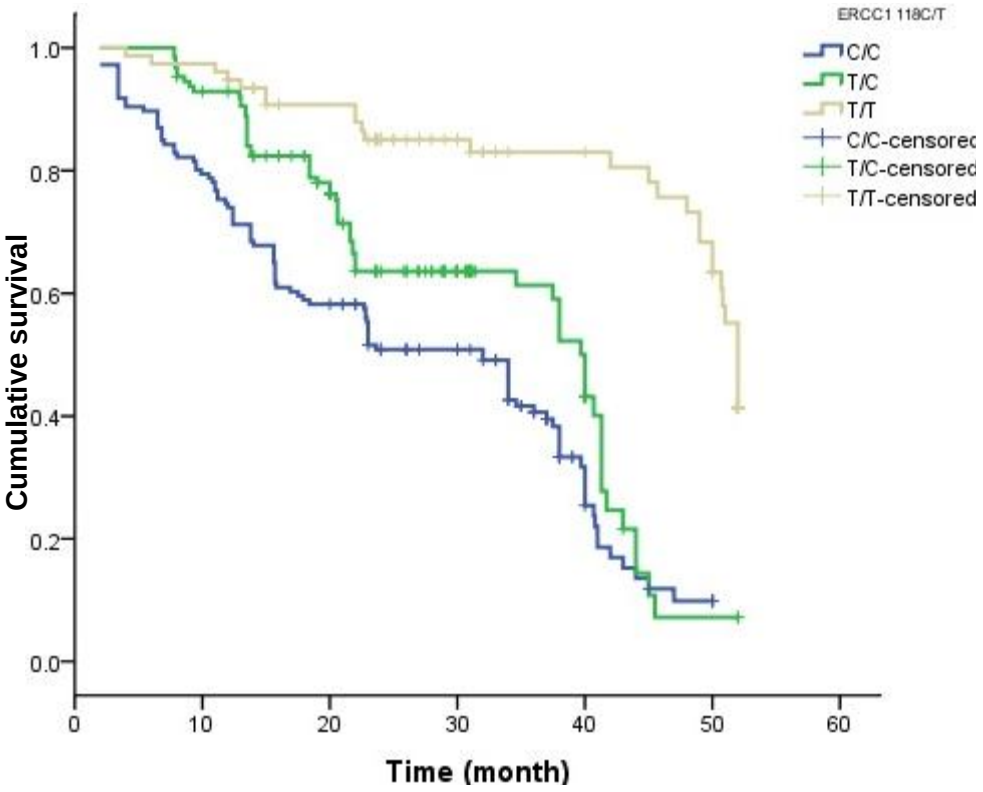

Figure 1. Survival of glioma by polymorphism in ERCC1 118C/T.

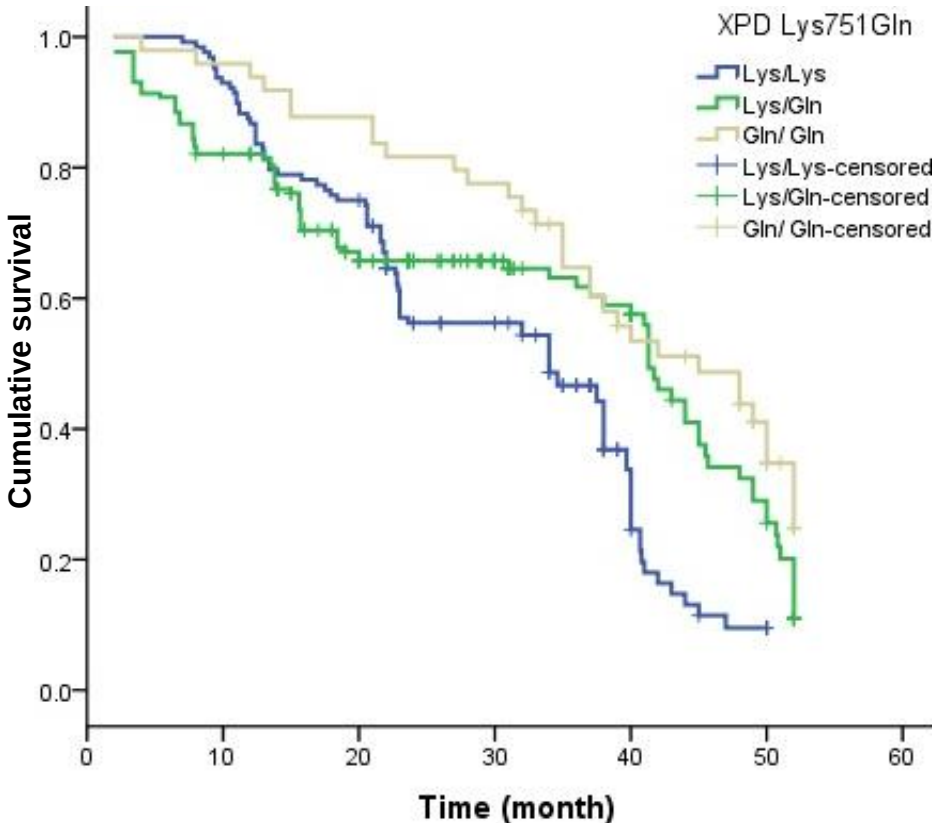

Figure 2. Survival of glioma by polymorphism in XPD Lys751Gln.

et al., 2011). The chemotherapy could induce the DNA damage of cancer cells, while the low activity of ERCC1 and XPD polymorphisms might influence the therapy outcome. In our study, we found that individuals carrying ERCC1 118T/T and XPD 751Gln/Gln genotypes could significantly reduce the risk of death from glioma, which provides solid evidence for the above hypothesis. Moreover, the genetic information on the polymorphisms and gene expression could play an important role in creating successful pharmacogenetic-guided chemotherapy. The use of rapid and sensitive PCR assays for diagnostic screening, coupled with ready accessibility to peripheral blood from patients with glioma, will help facilitate application of our study.

Among the limitations experienced in this study were: first, the patients recruited in this study might not represent for all glioma patients in our city and the findings from this study may not apply to the whole population in our city or other Chinese populations because it was conducted in a single setting. Secondly, because of practical difficulties, the longest follow up time lasted for 52 months, which was not long enough to assess the prognosis of glioma. Thirdly, the sample size may limit and may not have enough statistical power to find difference. In conclusion, however, our present data indicated that polymorphisms in ERCC1 118C/T(rs3212986) and XPD Lys751Gln(rs13181) have a role in the prognosis of glioma. Moreover, larger sample studies from Chinese population are still needed.

REFERENCES

Altaha R, Liang X, Yu JJ, Reed E (2004). Excision repair cross complementing-group 1: gene expression and platinum resistance. Int. J. Mol. Med. 14(6):959-970.

Azad AK, Bairati I, Samson E, Cheng D, Mirshams M, Qiu X, Savas S, Waldron J, Wang C, Goldstein D, Xu W, Meyer F, Liu G (2012). Validation of genetic sequence variants as prognostic factors in early-stage head and neck squamous cell cancer survival. Clin. Cancer Res. 18(1):196-206.

Chacko P, Rajan B, Joseph T, Mathew BS, Pillai MR (2005). Polymorphisms in DNA repair gene XRCC1 and increased genetic susceptibility to breast cancer. Breast Cancer Res. Treat 89 (1):15-21.

Giovannetti E, Pacetti P, Reni M, Leon LG, Mambrini A, Vasile E, Ghidini M, Funel N, Lucchesi M, Cereda S, Peters GJ, Cantore M (2011). Association between DNA-repair polymorphisms and survival in pancreatic cancer patients treated with combination chemotherapy. Pharmacogenomics., 12(12):1641-1652.

Ron E, Modan B, Boice JD Jr, Alfandary E, Stovall M, Chetrit A, Katz L (1988). Tumors of the brain and nervous system after radiotherapy in childhood. N. Engl. J. Med. 319 (16):1033-1039.

Ronen A, Glickman BW (2001). Human DNA repair genes. Environ. Mol. Mutagen, 37(3):241-283.

Rybárová S, Vecanová J, Hodorová I, Mihalik J, Čižmáriková M, Mojžiš J, Solár P, Benický M, Adamkov M, Mirossay L (2011). Association between polymorphisms of XRCC1, p53 and MDR1 genes, the expression of their protein products and prognostic significance in human breast cancer. Med. Sci. Monit. 17(12):BR354-363.

Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I(2005). Long-term follow up for brain tumour development after childhood exposure to ionising radiation for tinea capitis. Radiat. Res.163 (4):424-432.

Xu C, Wang X, Zhang Y, Li L (2011). Effect of the XRCC1 and XRCC3 genetic polymorphisms on the efficacy of platinum-based chemotherapy in patients with advanced non-small cell lung cancer. Zhongguo Fei Ai Za Zhi.14(12):912-917.

Zhang H, Li W, Franklin MJ, Dudek AZ (2011). Polymorphisms in DNA repair gene XRCC1 and skin cancer risk: a meta-analysis. Anticancer Res. 31(11): 3945-3952.