ORIGINAL ARTICLE

Excision Repair Cross-Complementation Group 1 (ERCC1) Polymorphism Predicted Platinum-Based Chemotherapy Treatment Outcome in Cholangiocarcinoma

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Background: Platinum-based chemotherapy is an effective cytotoxic treatment for many cancers. ERCC1 and ERCC2 are major enzymes involved in nucleotide excision repair (NER), influencing mRNA level and stability. ERCC1 polymorphism has been identified as a predictive biomarker for platinum treatment in several cancers. The prevalence of *ERCC1* rs11615, *ERCC1* rs3212986, *ERCC2* rs1799793, and *ERCC2* rs13181 are statistically significant in Japanese and Caucasian populations. However, data on Cholangiocarcinoma (CCA) are limited.

Objective: To investigate an associational study in ERCC1 and ERCC2 polymorphism and the clinical outcome of platinum-based therapy in cholangiocarcinoma.

Materials and Methods: The authors conducted a retrospective review of clinical data and analyzed genomic DNA from formalin-fixed paraffin-embedded tissue obtained from patients diagnosed with locally advanced or metastatic CCA who underwent palliative chemotherapy.

Results: Among 54 patients, those with the ERCC1 rs11615 heterozygous SNP (CT) exhibited a trend toward better overall survival compared to the wild type (CC), with 8.8 months versus 6.3 months, respectively. The hazard ratio (HR) was statistically significant in multivariate survival analysis (HR 0.47, 95% CI 0.23 to 0.94, p=0.032). These findings were also associated with improved objective response and disease control rates. No significant association was found between efficacy and ERCC1 rs3212986 (C>A), ERCC2 rs1799793 (C>T), or ERCC2 rs13181 (A>C) mutations.

Conclusion: The ERCC1 rs11615 heterozygous mutant showed prolonged survival, better response, and disease control rates.

Keywords: Cholangiocarcinoma; ERCC1; Polymorphism; Platinum-base; Survival; Response

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Cholangiocarcinoma (CCA) originated from biliary epithelial cells and is the second most common primary hepatic malignancy after hepatocellular carcinoma[1]. The incidence and mortality rate of CCA show substantial geographical variation. The northeast region of Thailand had the highest incidence rate, up to 85 per 100,000 people[1]. The standard chemotherapy for unresectable or metastatic disease is gemcitabine or 5-fluoropyrimidine (5-FU), usually combined with platinum-based chemotherapy[2-5]. Current CCA treatment problems are chemo-resistance, especially multidrug resistance, resulting in poor outcomes[6]. Therefore, biomarker-identified patients who would benefit from those agents are important.

Platinum compound alkylating agents, including cisplatin, carboplatin, and oxaliplatin, modulate several signal transduction pathways that lead to cell death, which is drug concentration dependence. They bind the DNA and form the bulky DNA helix-distorting adduct in intra- and interstrand crosslinks. Intrastrand crosslinks are repaired by nucleotide excision repair (NER). The NER pathway is

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a major DNA repair system that removes platinum adducts. This pathway involves many proteins in lesion recognition, excision, DNA synthesis, and ligation. Excision repair cross-complementary 1 (ERCC1) is a key protein involved in NER cells' process of repairing themselves by removing those damaged DNA by nucleotide excision repair (NER) enzymes. The excision repair cross-complementation group (ERCC) is the important rate-limiting step enzyme of NER[7]. A recent study showed that ERCC1 and ERCC2 play an important role in the NER pathway. Low expression of ERCC1 was a significant association with better tumor sensitivity to cisplatin and improved survival in many studies[8,9]. High tumoral expression of ERCC1 is associated with resistance to platinum-based chemotherapy[10]. A retrospective study of immunohistochemistry (IHC) stained in the resected specimen of CCA patients who received cisplatin and 5-FU found that patients who had negative ERCC1 had significantly longer overall survival in hilar and extrahepatic CCA[11].

ERCC1 and ERCC2 are two DNA repair genes on chromosome 19q13. Polymorphism of ERCC1 and ERCC2 related to ERCC expression. Polymorphism in ERCC1 include mainly ERCC1 rs11615 (C>T) , ERCC1 rs3212986 (C>A), ERCC2 rs1799793 (C>T), ERCC2 rs13181 (A>C). The ERCC1 rs11615 (C>T) was the most common Single-nucleotide polymorphisms (SNP) investigated in preclinical and clinical studies. The ERCC1 rs11615 SNPs caused a lower transcription rate and messenger ribonucleic acid (mRNA) levels, resulting in lower ERCC1 expression, but the association with the response rate and survival was inconsistent.(10) The polymorphism ERCC1 rs3212986 (C>A) is located in the 3' untranslated region and may affect mRNA stability, resulting in a decreased expression level. Patients who carried ERCC1 rs11615 (C>T), ERCC1 rs3212986 (C>A) mutation were associated with significantly improved overall survival and progression-free survival in many previous studies such as esophageal cancer, non-small cell lung cancer, and cervical cancer[8,9,12,13]. The ERCC2 gene is another gene that mediates DNA unwinding to initiate NER. Most ERCC2 mutations were located within or adjacent to helicase domains. ERCC2 rs1799793 (C>T) polymorphism causes an amino acid substitution from aspartic acid (Asp) to asparagine (Asn) at codon 312 (D312N) in exon 10[14]. The previous studies revealed that the levels of DNA adduct in T allele patients are higher compared with those in T allele individuals leading to reduce mRNA levels lead to a lower ability to repair the allele[15,16]. Moreover, it also increases synthesis enzyme activity and their ability to detoxify and excrete platinum-based agents, reducing the concentration of platinum-based agents in tumor cells[17]. Similarly, ERCC2 rs13181 (T>G) (Lys751Gln in exon 23) demonstrated that individuals with G alleles have a higher level of DNA adduct and lower repairability[16,18]. Recent data showed mutation of ERCC2 rs1799793 (C>T) and ERCC2 rs13181 (T>G) associated with predictor prognosis in platinum-based chemotherapy[17,19-21]. However, ERCC1 and ERCC2 polymorphism associated with platinum-based chemotherapy in cholangiocarcinoma were limited.

Therefore, we investigated an associational study in ERCC1 and ERCC2 polymorphism and the clinical outcome of platinum-based therapy in cholangiocarcinoma.

Materials and Methods

The present study was a retrospective study of patients diagnosed with locally advanced or metastatic CCA and received palliative chemotherapy in Srinagarind Hospital, Khon Kaen University, Thailand, between January 1, 2014, and December 31, 2018 - the chemotherapy including cisplatin, carboplatin, oxaliplatin, gemcitabine, 5-FU, or capecitabine. Exclusion criteria were patients who did not have available formalin-fixed paraffin-embedded (FFPE) tissue, received chemotherapy as adjuvant treatment, and combined hepatocellular carcinoma. Baseline characteristics were retrospective reviews for all patients. We assessed the response to chemotherapy in each patient according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Overall survival is calculated from the pathological report date to the day of death.

The study received ethical approval from the Khon Kaen University Ethics Committee for Human Research (HE631170).

Sample collection, DNA isolation, and genotyping

Our pathologist reviewed the FFPE specimen and collected the tissue from the tumor area. According to the manufacturer's instructions, genomic DNA was isolated with the QIAmp® DNA FFPE tissue (QIAGEN GmbH, Hilden, Germany). Assess the quantity and quality of genomic DNA by spectrophotometer (Thermo Scientific™ NanoDrop 2000c) absorbance at 260 nm purities calculated by A260/A280 ratio.

All polymerase chain reaction (PCR) contained 2 µL of patient genomic DNA, 12.5 µL TaqMan Genotyping Master Mix (TaqMan® SNP Genotyping Assays, Life Technologies, Carlsbad, CA, USA), 0.625 µL primers and probes, and 9.875 µL nuclease-free water for a final volume of 25 µL. The corresponding primers and probes were commercially available (Thermo Fisher Scientific Inc., Waltham, Massachusetts, United States), including ERCC1 rs11615 (C>T), ERCC1 rs3212986 (C>A), ERCC2 rs1799793 (C>T), ERCC2 rs13181 (A>C). Real-time PCR was performed on ABI QuantStudio™ 6 Flex for rs11615 and System LightCycler® 480 System using the following

conditions: Denature 95°C 10 min, annealing 95°C 15 sec, 60°C 1 min, 50 cycles.

Statistical analysis

The primary endpoint of this study is the overall survival (OS) comparison between each SNP. All statistical analysis was done using STATA, version 10.0. Descriptive statistics of baseline characteristics were reported as median and proportions. The factors that had a trend to affect OS by p-value <0.25 or clinically significant were selected to use in multivariate analysis. The median OS of each group was estimated using the Kaplan-Maier method. OS of patients who were alive or lost follow-up was censored at the time of the last contact to estimate the survival. Between-group differences in OS, hazard ratios (HR), and their 95% confidence intervals (CI) were calculated using a univariate Cox proportional hazards model. The adjusted HR was calculated by multivariate Cox survival analysis. The p-value less than 0.05 was considered as statistically significant. The objective response rate was reported in the descriptive statistics.

Results

FFPE tissue of 54 patients was investigated for DNA isolation and genotyping. Baseline characteristics are shown in Table 1. Age above 60 years old, ECOG performance status of 2, and receiving second-line chemotherapy had a trend to impact overall survival. The prevalence of ERCC1 rs11615 (C>T), ERCC1 rs3212986 (C>A), ERCC2 rs1799793 (C>T), and ERCC2 rs13181 (A>C) were shown in Tables 2 and 3, respectively. The genotypes distribution of ERCC1 rs11615 (X^2=0.67, p=0.716), ERCC1 rs3212986 (X^2=4.61, p=0.1), ERCC2 rs1799793 (X^2=0.27, p=0.877), ERCC2 rs13181 (X^2=0.27, p=0.877) were in Hardy-Weinberg equilibrium. The prevalence of ERCC1 rs11615, ERCC1 rs3212986, ERCC2 rs1799793, and ERCC2 rs13181 in the present study were statistically significant from Japanese and Caucasian populations.

For the patients who received platinum-based chemotherapy combined with either 5-FU or gemcitabine, the median overall survival was 8.1 months. The ERCC1 rs11615 heterozygous mutant (CT) had a longer median OS than wild type (CC) (8.8 vs. 6.3 months, HR 0.70 (95% CI, 0.40 to 1.23), but there was no statistically significant (p=0.220) as showed in Table 4 and Figure 1. For ERCC1 rs3212986, the homozygous variant (AA) and heterozygous variant (CA) had shorter median OS than wild type (CC) but there were not statically significant (6.2 vs. 8.0 vs. 9.5, respectively: HR 2.21 (95% CI 1.002 to 4.87, p=0.049) and HR 1.80 (95% CI 0.95 to 3.43, p=0.072)).

In the multivariate survival analysis adjusted with age group, ECOG performance status, stage (locally advanced or metastasis), first-line chemotherapy regimen, and receiving second-line chemotherapy, ERCC1 rs11615 heterozygous mutanat (CT) had statistically significant longer OS compared with wild-type, adjusted HR 0.47 (95% CI, 0.23 to 0.94) (Table 5). Besides longer OS, the ERCC1 rs11615 heterozygous genotype (CT) also had a better response rate (15% vs. 0%) and disease control rate (55% vs. 25%) compared with the wild type, as shown in Table 6.

Discussion

The prevalence of ERCC1 rs11615, ERCC1 rs3212986, ERCC2 rs1799793, and ERCC2 rs13181 in the present study were statistically significant from Japanese and Caucasian populations. The response rate of platinum-based therapy may have a different outcome from other populations. The author's study on the tumor genomic DNA suggested that ERCC1 rs11615 was associated with overall survival. Patients with heterozygous SNP (CT) had a better response to platinum-based chemotherapy and were associated with significantly prolonged overall survival by the multivariate survival analysis (Figure 2).

Although the important role of ERCC1 in the NER was significant, the technique to determine the ERCC1 expression and application to clinical practice was challenging. IHC technique was more familiar and more available, but the result may vary by type of antibodies and individual pathologist experiences. Several retrospective studies of CCA concluded that lower or negative ERCC1 protein expression determined by IHC was a prognostic factor associated with good survival[11,26]. Nevertheless, recent data from a large retrospective study on non-small cell lung cancer with currently available antibodies did not precisely detect the unique functional ERCC1 isoform. They summarized that it is not useful as a predictive biomarker of response to chemotherapy and should be carefully evaluated in future studies[27].

The present study decided to use the tumor genomic DNA analysis for SNPs, which is more complicated but more constant and reproducible. ERCC1 rs11615 variant reduced the transcription and mRNA levels of ERCC1, resulting in lower ERCC1 expression[10]. ERCC1 rs11615 transition substitution in ERCC1 exon 4 caused a silent mutation at codon 118 coded for the same amino acid, asparagine. A previous study in ovarian cancer cell lines found that this transition converts a common codon usage (AAC) to an infrequent codon usage (AAT). In contrast, the frequency of use is reduced by approximately 50%. The ERCC1 mRNA was markedly reduced and less proficient at cisplatin-DNA adduct repair (0.86 pg/microgram DNA over 6 h vs. 2.7 pg/microgram DNA) than the wild-type. These data suggested the possibility that this specific ERCC1 polymorphism may be associated with reduced DNA repair capacity in human

Table 1. Baseline characteristics

Baseline characteristic	n (%)	Median OS (IQR, month)	HR (95% CI)	p-value
Age				
≤60 years	33 (61.1)	9.0 (5.8,12.7)	-	-
>60 years	21 (38.9)	6.9 (3.3, 10.0)	1.62 (0.90 to 2.91)	0.107
Sex				
Male	39 (72.2)	8.1 (4.8, 10.9)	-	-
Female	15 (27.8)	10.3 (4.5 to 13.4)	0.73 (0.40 to 1.36)	0.324
ECOG				
0-1	48 (88.9)	8.8 (4.7, 12.6)	-	-
2	6 (11.1)	7.8 (3.7, 8.1)	2.31 (0.94 to 5.68)	0.067
BMI (kg/m^2) median, IQR	22.6 (20.0, 25.1)	8.1 (4.7, 12.0)	1.00 (0.92 to 1.09)	0.948
Comorbidity				
No	39 (72.2)	8.9 (4.7,12.0)	-	-
Yes	15 (27.8)	8.1 (4.5, 10.9)	0.74 (0.39 to 1.45)	0.379
Prior curative resection				
No	51 (94.4)	8.1 (4.5,12.0)	-	-
Yes	3 (5.6)	11.5 (10.9 to 12.9)	0.68 (0.21 to 2.21)	0.525
CA19-9 (U/mL) median, IQR	125.8 (16.8, >1,000)	8.1 (4.7, 12.0)	1.00 (0.9995 to 1.0008)	0.693
CEA (ng/mL) median, IQR	10.5 (4.1, 32.00	8.1 (4.7, 12.0)	1.01 ((1.01 to 1.02)	0.000
Type				
Intrahepatic	50 (92.6)	8.0 (4.7, 12.0)	-	-
Perihilar	4 (7.4)	9.0 (4.1, 10.5)	0.58 (0.18 to 1.88)	0.366
Stage				
Locally advanced	21 (39.6)	6.9 (4.5, 10.1)	-	-
Metastasis	32 (60.4)	8.5 (4.8, 11.9)	0.80 (0.45 to 1.41)	0.442
Metastatic site				
Liver	14 (25.9)	5.8 (3.2, 10.9)	1.30 (0.69 to 2.45)	0.421
Peritoneum	12 (22.2)	9.1 (5.2, 12.9)	0.83 (0.43, 1.59)	0.566
Lung	9 (16.7)	8.9 (7.2, 11.6)	0.98 (0.47 to 2.01)	0.949
Bone	10 (18.5)	7.8 (5.8, 11.6)	1.10 (0.55 to 2.22)	0.781
Pathologic grade				
Well-differentiated	10 (18.5)	9.2 (5.8 to 12.0)	-	-
Moderate-differentiated	3 (5.6)	11.6 (4.5,12.7)	0.95 (0.26 to 3.48)	0.941
Poorly differentiated	1 (1.9)	4.1	4.66 (0.55 to 39.28)	0.157
Unknown	40 (74.1)	8.0 (4.7, 11.9)	0.97 (0.48 to 1.96)	0.934
First-line chemotherapy				
5-Fluorouracil-Platinum	25 (46.3)	8.1 (4.1,2.9)	-	-
Gemcitabine-platinum	29 (53.7)	8.5 (5.8, 11.6)	1.19 (0.68 to 2.11)	0.538
Second-line chemotherapy				
No	47 (87.0)	8.1 (4.5, 11.9)	-	-
Yes	7 (13.0)	10.9 (7.2,13.2)	0.48 (0.19 to 1.23)	0.127

*IQR=Interquartile range

ovarian cancer cells as a consequence of the reduction in the translation of ERCC1 mRNA into protein[28,29], whether these cell-lines findings could be translated into clinical significance remained a controversy.

Our study found that ERCC1 rs11615 heterozygous mutant was associated with more prolonged survival and better response. There were two smaller, same-target SNPs studied in CCA. Of the 33 patients in the study by Pacetti et al. in Italy, almost 90 percent were SNP variants, which differs from our study. Patients with ERCC1 rs11615 wild-type (CC), heterozygous SNP (CT), and homozygous SNP (TT) had a median OS of 9.2, 18.9 months, and not reach respectively, which correlated with our study[30]. A smaller study of 26 patients in central Thailand showed the same SNP distribution as ours. However, the response rate compared between SNPs was reversed with our study;

Table 2. Prevalence of ERCC1 rs11615 (C>T) and ERCC1 rs3212986 (C>A) for the patients in this study

Ethnic group	ERCC1 rs3212986 genotype frequencies (%)					ERCC1 rs11615 genotype frequencies (%)					Ref.
	N	CC	CA	AA	p-value[a]	N	CC	CT	TT	p-value[a]	
Thai	54	21 (38.89)	23 (42.59)	10 (18.52)		54	25 (46.30)	28 (51.85)	1 (1.85)		This study
Chinese	213	104 (48.83)	91 (42.72)	18 (8.45)	0.079	213	117 (54.93)	82 (38.50)	14 (6.57)	0.173	Ni M, 2014[22]
Japanese	125	77 (61.60)	42 (33.60)	6 (4.80)	0.002*	63	30 (47.62)	23 (36.51)	10 (15.87)	0.022*	Hirakawa H, 2020[23]
											Kumamoto K, 2013[24]
Taiwanese	58	29 (50.00)	18 (31.03)	11 (18.97)	0.407	58	23 (39.66)	33 (56.90)	2 (3.44)	0.710	Liao W-Y, 2018[25]
Caucasian	706	399 (56.52)	257 (36.40)	50 (7.08)	0.003*	705	107 (15.18)	324 (45.96)	274 (38.86)	<0.001*	Zhao H, 2008[18]

* The mean difference is significant at the 0.0125 level; [a] Adjustment for multiple comparisons: Bonferroni correction.

Table 3. Prevalence of ERCC2 rs1799793 (C>T), ERCC2 rs13181 (A>C) for the patients in this study

Ethnic group	ERCC2 (rs1799793) genotype frequencies (%)					ERCC1 (rs11615) genotype frequencies (%)					Ref.
	N	CC	CT	TT	p-value[a]	N	CC	CT	TT	p-value[a]	
Thai	53	46 (86.79)	7 (13.21)	-		53	46 (86.79)	7 (13.21)	-		This study
Chinese	213	182 (85.45)	26 (12.20)	5 (2.35)	0.525	213	176 (82.63)	35 (16.43)	2 (0.94)	0.649	Ni M, 2014[22]
Japanese	125	118 (94.40)	7 (5.6)	-	0.226	125	117 (93.60)	8 (6.40)	-	0.327	Hirakawa H, 2020[23]
Taiwanese	58	54 (93.10)	4 (6.90)	-	0.539	58	48 (82.76)	10 (17.24)	-	0.841	Liao W-Y, 2018[25]
Caucasian	707	290 (41.02)	335 (47.38)	82 (11.60)	<0.001*	707	289 (40.88)	330 (46.68)	88 (12.44)	<0.001*	Zhao H, 2008[18]

* The mean difference is significant at the 0.0125 level; [a] Adjustment for multiple comparisons: Bonferroni correction.

Table 4. Overall survival of the patients according to ERCC1 rs11615 (C>T) , ERCC1 rs3212986 (C>A)

	All population	ERCC1 rs11615 (C>T)			ERCC1 rs3212986 (C>A)		
		CC	CT	TT	CC	CA	AA
	n=54	n=25	n=28	n=1	n=21	n=23	n=10
Median OS (IQR, month)	8.1 (4.7, 12.0)	6.3 (3.7, 12.0)	8.8 (5.8, 11.9)	8.9	9.5 (6.5, 13.4)	8.0 (4.1, 10.9)	6.2 (2.7, 9.2)
HR (95% CI)	-	HR 1.00 (Control)	HR 0.70 (0.40 to 1.23)	-	HR 1.00 (Control)	HR 1.80 (0.95 to 3.43)	HR 2.21 (1.002 to 4.87)
p-value	-	-	p=0.220	-	-	p=0.072	p=0.049
6-month OS (95% CI)	-	56.0% (34.8 to 72.3)	75.0% (54.6 to 87.2)	100%	76.2% (51.9 to 89.3)	60.9% (38.3 to 77.4)	60% (25.3 to 82.7)
12-month OS (95% CI)	-	23.3% (9.1 to 41.3)	25.0% (11.0 to 41.8)	0%	38.1% (18.3 to 57.8)	10.4% (1.9 to 27.7)	20% (3.0 to 47.5)

the authors summarize no statistical difference between SNPs (limited by sample size)[31]. More data from many prospective and retrospective studies were collected mainly in DNA from peripheral white blood cells of non-small cell lung cancer, ovarian cancer, and colorectal cancer who received platinum-based chemotherapy, resulting in mixed outcomes: positive, negative, and no significant associations[10,32]. We found no statistically significant association between less common use SNPs study and treatment efficacy in ERCC1 rs3212986 (C>A), ERCC2 rs1799793 (C>T), ERCC2 rs13181 (A>C) genotype.

Limitations, We did not pair the genomic DNA from the archival tumor tissue and germline genomic DNA. This could limit the conclusion of whether these findings were seen only in the tumor SNPs or extrapolated to germline SNPs. However, genotyping DNA from FFPE specimens is highly concordant with genotyping germline DNA from the whole blood sampling[23]. The other limitations included retrospective study design, sample size, and extensive missing data. Future prospective research should include

the genomic DNA from both germline and tumor tissue.

Conclusion

ERCC1 rs11615 mutant allele are associated with efficacy in CCA patients receiving platinum-based chemotherapy. More prolonged survival, better response, and disease control rate were observed in ERCC1 RS11615 heterozygous SNP (CT).

What is already known on this topic?

ERCC1 polymorphism has been identified as a predictive biomarker for platinum treatment in several cancers.

What this study adds?

CCA is our common cancer and the ERCC1 rs11615 heterozygous mutant showed better outcomes in this cancer type.

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Potential conflict of interest

The authors declare no conflict of interest.

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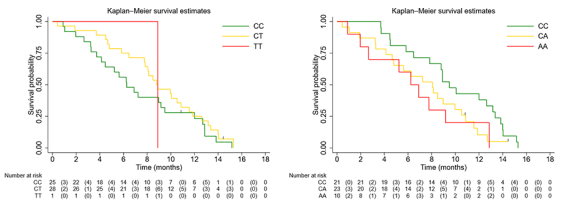

Figure 1. Kaplan-Meier estimates the overall survival according to the ERCC1 rs11615 and ERCC1 rs3212986.

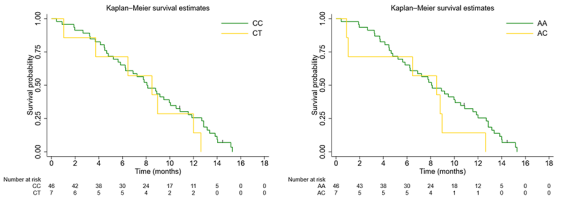

Figure 2. Kaplan-Meier estimates the overall survival according to ERCC2 rs1799793 and ERCC2 rs13181.

Table 5. Multivariate survival analysis* of OS compare between wild-type and variant of ERCC1 rs11615, ERCC1 rs3212986

Variables	Adjusted HR** (95% CI)	p-value
ERCC1 rs11615 CT	0.47 (0.23 to 0.94)	0.032
ERCC1 rs3212986 CA	1.83 (0.96 to 3.51)	0.067
ERCC1 rs3212986 AA	1.99 (0.88 to 4.51)	0.100

* Factors included in the multivariate survival analysis: Age group, ECOG performance status, stage, first-line chemotherapy regimen, and receiving second-line chemotherapy.

** HR compared with wild-type ERCC1 group.

Table 6. Response rate to first-line platinum-base chemotherapy in ERCC1 rs11615 and ERCC1 rs3212986

Response rate	ERCC1 rs11615 (C>T)		ERCC1 rs3212986 (C>A)		
	CC	CT	CC	CA	AA
PR, n (%)	0 (0.0)	3 (15.0)	3 (18.8)	0 (0.0)	0 (0.0)
SD, n (%)	3 (25.0)	8 (40.0)	6 (37.5)	4 (33.3)	1 (20.0)
PD, n (%)	9 (75.0)	9 (45.0)	7 (43.6)	8 (66.7)	4 (80.0)
DCR, n (%)	3 (25.0)	11 (55.0)	9 (56.3)	4 (33.3)	1 (20.0)
Unknown, n	13	8	5	11	5

* PR=partial response; SD=stable disease; PD=progressive disease; DCR=disease control rate

Table 7. Overall survival of the patients according to ERCC2 rs1799793, ERCC2 rs13181

	All population	ERCC2 rs1799793 (C>T)		ERCC2 rs13181 (A>C)	
		CC	CT	AA	AC
	n=53	n=46	n=7	n=46	n=7
Median OS (IQR), month	8.1 (4.7, 12.0)	8.1 (4.7, 12.7)	8.5 (3.7, 12.0)	8.1 (4.7, 12.7)	8.5 (1.0, 9.0)
HR (95% CI)	-	HR 1.00 (Control)	HR 1.41 (0.65 to 3.17)	HR 1.00 (Control)	HR 1.70 (0.75 to 3.85)
p-value	-	-	p=0.413	-	p=0.206
6-month OS (95% CI)	-	65.2 (49.6 to 77.0)	71.4 (25.8 to 92.0)	65.2 (49.6 to 77.0)	71.4 (25.8 to 92.0)
12-month OS (95% CI)	-	25.6 (14.1 to 38.9)	14.3 (0.7 to 46.5)	25.5 (14.0 to 38.8)	14.3 (0.7 to 46.5)

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