Predictive and prognostic value of excision repair cross-complementing group 1 by multi-omics on the outcomes in patients with advanced gastric cancer

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Abstract

Background

To define the optimal chemotherapy regimen for each patient we therefore used tissue from patients to identify molecular prognostic or predictive biomarkers.

Methods

Endoscopic biopsy specimens from primary lesions and surgical specimens on a phase III trial in patients with unresectable advanced or recurrent gastric cancer treated with docetaxel with cisplatin plus S-1 (DCS) or cisplatin plus S-1 (CS), were collected. We measured the mRNA expression of ERCC1 and analyzed SNPs in GSTP1 and ERCC1.

Results

Low ERCC1 expression was associated with favorable prognosis for overall survival, OS by multivariable analysis ($P = 0.001$). There were significant interactions between the two treatment arms of DCS and CS, and ERCC1 mRNA expression. In patients with low ERCC1 expression of a favorable prognosis, DCS therapy was inferior to CS ($P = 0.046$). In addition to GSTP1 rs1695 (HR 1.728), ERCC1 rs3212980, ERCC1 rs2298881, ERCC1 rs3212964 with high expression of ERCC1 mRNA were associated with significantly worse prognosis with regard to OS.

Conclusions

ERCC1 mRNA is an independent prognostic factor and predictive marker that can be used to guide the addition of docetaxel. The SNPs of ERCC1 and GSTP1 could be also prognostic or predictive factors.

Clinical Trial Number: UMIN000007652

INTRODUCTION

Fluoropyrimidine and platinum-based combination therapies are the most commonly used and acceptable first-line therapies for patients with HER-2 negative gastric cancer worldwide [1]. The V325 study demonstrated the superiority of triplet chemotherapy using docetaxel plus cisplatin and 5-fluorouracil (5-FU) over doublet chemotherapy with cisplatin and 5-FU for patients with advanced gastric cancer [2]. This triplet regimen has not been accepted globally as a standard palliative treatment because it elicits severe neutropenia and confers a small survival advantage. JCOG 1013 trial showed that the triplet therapy with docetaxel added to cisplatin and S-1 (DCS) did not prolong overall survival (OS) and progression-free survival (PFS) in patients with unresectable advanced or recurrent gastric cancer compared with the doublet of cisplatin and S-1 (CS) [3]. Poor performance status (PS), peritoneal metastasis, liver metastasis, histological type, and disease status (unresectable advanced or recurrent) are established clinical prognostic factors for metastatic gastric cancer [4, 5]. On the other hand,
perioperative triplet therapy with docetaxel, fluoropyrimidine, and oxaliplatin showed survival benefit for patients with locally advanced resectable gastric cancer [6, 7]. These mixed results show that a better understanding of biological predictive or prognostic markers of conventional cytotoxic agents is required. Armed with this knowledge, physicians then can give patients the optimal drugs to prolong their survival and improve their quality of life. This is especially important for the use of cytotoxic drugs, which are not always effective in every patient and often cause severe adverse events.

Excision repair cross-complementation group 1 (ERCC1) is an important component of the nucleotide excision repair pathway which repairs DNA intra-strand, inter-strand, and DNA-protein crosslinks caused by cisplatin. DNA repair systems allow cells to overcome the DNA damage induced by chemotherapy [8]. In the JCOG9912 trial, low ERCC1 mRNA expression was a significant independent favorable prognostic factor in patients with metastatic gastric cancer who received first-line chemotherapy with 5-FU monotherapy, S-1 monotherapy, and cisplatin plus irinotecan [9]. Low mRNA levels of ERCC1 in primary gastric cancer have been associated with a higher overall response rate and longer survival following cisplatin treatment [9–14]. The expression of ERCC1 mRNA was suggested as a predictive and prognostic marker in resectable gastric cancer patients receiving chemotherapy. Providing complementary roles to ERCC1, X-ray repair cross-complementing group (XRCC1) is critical mediator of base excision repair and single-strand break repair [15, 16].

Single nucleotide polymorphisms (SNPs) ERCC1 rs3212986, rs2298881, rs11615, XRCC1 rs25487, and rs1695 in glutathione S-transferase pi 1 (GSTP1; an enzyme that is involved in cytosolic platinum detoxification [16, 17]), have been suggested as prognostic markers in preclinical studies [18–22]. The ERCC1 genotypes had no significant association with OS in patients who received perioperative therapy with epirubicin, cisplatin, and 5-FU (ECF) in the MAGIC trial [23]. However, patients with a TYMS2R/2R genotype derived a larger benefit from perioperative ECF than patients with TYMS3R genotypes [23]. Although low ERCC1 protein expression may be a better prognostic marker, the lack of adequate commercially available antibodies to detect the active ERCC1 subtype has limited the interpretation of immunohistochemical studies [24–26]. Therefore, we designed the current study to identify differences in survival and tumor regression after CS or DCS therapy. By taking a multi-omics approach, our aim was to quantify the real-world utility of these candidate molecular markers in clinical practice.

MATERIALS AND METHODS

Patients were randomly assigned (1:1) to receive DCS (docetaxel 40 mg/m² and cisplatin 60 mg/m² on day 1 intravenously, and S-1 40–60 mg twice a day orally for 2 weeks, every 4 weeks) or CS (cisplatin 60 mg/m² intravenously on day 8, and S-1 40–60 mg orally twice a day for 3 weeks, every 5 weeks) in the JCOG1013. Written informed consent to be enrolled in JCOG1013 was obtained before registration and the opportunity to refuse to provide tumor samples was provided through web sites of the National Cancer Center and the Japan Clinical Oncology Group (JCOG) according to the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects. The protocol of this translational study was approved by the institutional review board of the National Center for Global
Health and Medicine and each participating hospital and complied according to the criteria of REMARK (reporting recommendations for tumor marker prognostic studies [27]).

For the analysis, 5 × 10-µm sections or 10 × 4- or 5-µm sections were prepared from formalin-fixed paraffin embedded tumor tissues (FFPE). The tumor cells on the sections of interest were selectively isolated by macrodissection. *ERCC1* and *TYMS* and an internal reference gene (β-actin) were quantified with a fluorescence-based real-time detection method (LightCycler96 System and FastStart essential DNA Probes Master, Roche Diagnostics, Rotkreuz, Switzerland). The primers and probes used have been described previously [13]. Gene expression values (relative mRNA levels) are expressed as quantification cycle (Cq) ratios (differences between Cq values) between the genes of *ERCC1* or *TYMS* and an internal reference gene (β-actin) [28, 29].

The NCC Oncopanel test is a hybridization capture-based NGS assay designed to examine mutations, amplifications, and homozygous deletions of the entire coding region of 123 genes of clinical or preclinical relevance, along with rearrangements of 13 oncogenes included in the panel [30]. We modified the NCC Oncopanel for pharmacogenetic analysis to examine 66 SNPs in *DPYD, VEGFA, ABCB1, PRKDC, MGMT, GSTP1, ACRV, TYMS, XRCC1, POLR1G*, and *ERCC1*. Immunohistochemical staining of ERCC1 was performed using antibody 9D11 [31] and an Autostainer Link 48 device (Agilent, Santa Clara, CA). The evaluation area was limited to the region where gastric cancer cells were present in the total tissue of biopsy specimens, and in approximately three locations identified by low magnification (objective lens x4) of the surgical resection samples. The staining intensity was graded on a scale of 0–3. The expression of ERCC1 protein in cancer cells was normalized to the average ERCC1 nuclear staining intensity in intraregional vascular endothelial cells, which was set at 2. Thus, cancer cells expressed similar levels if their average staining intensity was 2, stronger expression if the value was 3, weaker if the value was 1, and were considered negative with a staining intensity of 0. The strongest intensity of ERCC1 expression of cancer cells in the region was measured.

**Statistical analysis**

The gene expression levels of *ERCC1* and *TYMS* were categorized into low and high groups by the median or an optimal cutoff value based on a SNP analysis to assess the associations between gene expression levels and OS, and PFS, and response rate. Categorical data were compared using Fisher’s exact test. Survival function was estimated with the Kaplan–Meier method, and differences between survival functions were compared with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) based on a Cox proportional hazards model were used to provide quantitative summaries of the gene expression data. Variables for the multivariable analysis included the genes with expression levels (high or low) that showed associations in the univariable analyses in this study, as well as the patient’s background, such as Eastern Cooperative Oncology Group (ECOG) PS, age, sex, number of metastatic sites, previous gastrectomy, presence or absence of target lesions according to RECIST version 1.0, histological classification (differentiated/undifferentiated) [32], and presence or absence of peritoneal metastasis. All reported *P*-values are two-sided, and the level of statistical significance was set
at $P<0.05$. All analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Relationship between ERCC1 and TYMS expression and survival

Tissue samples for this study were collected from 523 endoscopic biopsy specimens and 136 surgical specimens taken before the treatment of 741 randomized patients in JCOG1013 (Supplemental Fig. 1). The baseline characteristics were equally distributed among the subsets for ERCC1 and TYMS. A univariable analysis of the whole study population showed that both OS (HR, 0.861; 95% CI, 0.703–1.054; $P=0.147$) and PFS (HR, 0.882; 95% CI, 0.726–1.071; $P=0.205$) in the low ERCC1 mRNA groups were generally better than those in the high ERCC1 mRNA groups. There were significant interactions between the two treatment arms of DCS and CS, and ERCC1 mRNA expression (Table 1). High ERCC1 mRNA expression was significantly associated with worse prognosis, and DCS was inferior to CS in patients with low ERCC1 mRNA expression who had a better prognosis (Fig. 1). The response rates of CS and DCS were similar: 43% (47/109) and 36% (37/104) in the ERCC1-mRNA high group, and 29% (30/103) and 37% (40/109) in the ERCC1-mRNA low group. There were no significant differences in OS or PFS according to the expression of TYMS. Multivariable analyses for survival with ERCC1 mRNA expression and clinical characteristics showed that independent prognostic factors were ERCC1 mRNA and ECOG PS for OS, and ERCC1 mRNA and peritoneal metastasis for PFS (Table 2).

Relationship between ERCC1 mRNA and protein expression

There was no statistically significant correlation between ERCC1 Cq ratio and protein expression. The protein staining intensities (scale 0–3) in the ERCC1 mRNA-high group were 3 in 32/142 (23%), 2 in 84/142 (46%), 1 in 20/142 (38%), and 0 in 6/142 (4%). Staining intensities in the ERCC1-mRNA low group were 3 in 51/196 (26%), 2 in 98/196 (54%), 1 in 33/196 (17%), and 0 in 14/196 (7%). ERCC1 expression had no predictive and prognostic significance with regard to OS, PFS or tumor shrinkage.

ERCC1, XRCC1, and GSTP1 SNPs as prognostic factors

Genomic analysis using the NCC Oncopanel was performed on 111 surgical specimens and 13 endoscopic biopsy samples; most patients were postoperative recurrent cases. DCS was superior to CS for patients with recurrent gastric cancer after gastrectomy in terms of OS (21.9 months [95%CI, 17.9–26.3] vs 15.9 months [12.9–19.0], HR = 0.64 [0.45–0.90], $P=0.0095$), but not superior in patients with unresectable advanced gastric cancer (Supplemental Fig. 2MST, 13.0 months [11.9–14.3] vs 15.0 months [14.1–16.1], HR = 1.14 [0.963–1.36], $P=0.127$). There were significant differences between the baseline patient characteristics of unresectable advanced and recurrent gastric cancer regarding PS 1 (37% vs. 25%), only one metastatic site (38% vs. 66%), liver metastasis (31% vs. 21%), and bone metastasis (5% vs. 10%). Thus, patients with recurrent gastric cancer had more favorable prognostic factors than those with unresectable advanced gastric cancer. Among the 124 patients for whom data were available, DCS
was superior to CS ($P<0.01$). There were no differences in the distribution of \textit{ERCC1} mRNA expression between patients with unresectable advanced and those with recurrent gastric cancer. The prognostic values of \textit{ERCC1}, \textit{XRCC1}, and \textit{GSTP1} in patients treated with DCS or CS are shown in Table 3. \textit{ERCC1} rs3212964 (HR 1.533), \textit{ERCC1} rs2298881 (HR 1.525), and \textit{GSTP1} rs1695 (HR 2.336) were significant prognostic factors with regard to PFS. The \textit{ERCC1} rs3212980 TT, rs3212964 TT, rs11615 AA, rs3212948 GG, and rs2298881 AA alleles tended to have higher mean values of \textit{ERCC1} mRNA expression when compared with the reference alleles. Other remarkable HRs of DCS vs CS in terms of OS were 0.259 in \textit{DPYD} rs2297595 TC (vs 0.514 in TT), 1.777 in \textit{ABCB1} rs7787082 AA (vs 0.435 in GA and 0.426 in GG), 0.237 in \textit{XRCC2} rs1799782 AA (vs 0.499 GA and 0.678 in GG) (Supplemental Table 2).

**ERCC1, XRCC1, and GSTP1 SNPs as predictive factors**

\textit{ERCC1}, \textit{XRCC1}, \textit{GSTP1} SNPs were predictive of the benefits of DCS or CS in terms of OS and PFS (Table 4). When compared with each reference allele, the \textit{ERCC1} rs3212980 TT, rs3212964 TT, rs11615 AA, rs3212948 GG and rs2298881 AA alleles tended to have larger HR for both OS and PFS in the DCS-treated patients versus those treated with CS. Patients with \textit{GSTP1} GG who were treated with DCS had a shorter OS. The response rates in the CS and DCS groups were 20% vs. 27% in \textit{ERCC1} rs3212980 TT, 6% vs. 24% in rs3212964 TT, 0% vs. 29% in rs11615 AA, 0% vs. 29% in rs3212948 GG, and 6% vs. 25% in rs2298881 AA.

**Intra-tumoral gene mutation and outcomes**

\textit{TP53} mutation was observed in 43% of cases, \textit{ARID1A} in 12%, \textit{PIK3CA} in 8.1%, \textit{RHOA} in 7.3%, \textit{APC} in 6.5%, \textit{BRCA2} in 4.8%, \textit{KRAS} in 4.8%, \textit{SMAD4} in 4.8%, \textit{MSH6} in 2.4%, \textit{MLH1} in 0.8%, and \textit{MSH2} in 0.8% (Fig. 2). \textit{TP53} mutational status had no significant impact on OS. There was a tendency of poorer OS in patients with \textit{RHOA}, \textit{SMAD4}, or microsatellite instability- high (\textit{MSH6}/\textit{MLH1}/\textit{MSH2}) genetic alterations.

**DISCUSSION**

DNA repair capacity is a major determinant of cisplatin resistance, with \textit{ERCC1} protein playing an essential role in nucleotide excision repair. Here, we found that patients with high \textit{ERCC1} expression had a poorer overall survival than those with low \textit{ERCC1} expression. The DCS treatment regimen was inferior to CS in patients with low \textit{ERCC1} expression and a favorable prognosis. Therefore, the triplet therapy is not required in this patient subset. Recurrent gastric cancer patients with \textit{ERCC1} rs3212964, \textit{ERCC1} rs2298881, or \textit{GSTP1} rs1695 SNPs had higher \textit{ERCC1} expression and had a worse OS. Moreover, DCS was inferior to CS in terms of PFS if patients had the \textit{ERCC1} rs11615 AA or \textit{ERCC1} rs3212948 GG SNPs. DCS was also inferior to CS in terms of OS in patients with the \textit{XRCC1} rs25487 TT or \textit{GSTP1} rs1695 GG SNPs. Our data confirm that \textit{ERCC1} expression, as well as specific SNPs in \textit{ERCC1}, \textit{XRCC1}, and \textit{GSTP1}, are significant prognostic indicators that could guide the choice between DCS or CS treatment regimens.

Our previous ancillary investigation of another randomized controlled trial, JCOG9912, showed that low \textit{ERCC1} expression was a significant independent favorable prognostic factor in patients with advanced
gastric cancer who were also receiving first-line chemotherapy. The baseline patient characteristics were different between JCOG9912 and the current JCOG1013 trial. About 50% of analyzed patients in JCOG1013 had peritoneal metastasis compared with 27% in JCOG9912. The frequency of liver metastasis was 30% in this study but 48% in JCOG9912. Although the treatment regimens were different (CS and DCS were used in JCOG1013 whereas 5-FU monotherapy, S-1 monotherapy, or cisplatin plus irinotecan combination therapy were used in JCOG9912) the prognostic effect of \textit{ERCC1} expression was still evident in both cases. The \textit{ERCC1} rs3212964 and \textit{ERCC1} rs2298881 SNPs were found in patients with higher \textit{ERCC1} expression, which explains why they were associated with a poorer prognosis. Because genotyping from FFPE breast cancer specimens was significantly concordant with genotyping from germline DNA, the effects of cytotoxic chemotherapy and its impact on survival can be predicted by DNA analysis of blood or buccal mucosa [33].

Since high \textit{ERCC1} expression is an indicator of poor prognosis, it has been a challenge to show the superiority of alternative combination therapies without platinum with regard to survival [14, 34]. From our results, some patients with low \textit{ERCC1} expression have a good prognosis, and this is compromised if they are given the more toxic triplet therapy. Hence, administration of DCS to patients with an otherwise favorable prognosis, particularly those who are eligible for curative resection, should be avoided.

Commercially available methods to evaluate \textit{ERCC1} mRNA expression status are warranted, as they will guide the choice of triplet DCS or doublet CS, which in turn will reduce the incidence of toxicity-related death and will improve patients’ quality of life. S-1 was effective in \textit{ERCC1}-high patients with resectable stage II or III gastric cancer after surgery in the adjuvant setting. However, S-1 monotherapy did not impart a statistically significant survival benefit in \textit{ERCC1}-low patients in the ACTS-GC trial [35]. Therefore, \textit{ERCC1} mRNA expression could be a predictive marker in the adjuvant setting. Thus, \textit{ERCC1} is not only related to the resistance of cisplatin but other chemotherapeutic agents. The results of our present study, which show that DCS is more effective than CS in \textit{ERCC1}-high patients, are consistent with these previously published data.

The \textit{ERCC1} gene generates four isoforms designated 201, 202, 203, and 204 by alternative splicing. Currently available antibodies such as 8F1 cannot discriminate between these isoforms and thus cannot guide therapeutic decision-making regarding cisplatin combined therapy in patients with non-small-cell lung cancer; this requires specific detection of the unique functional \textit{ERCC1}-202 isoform [26]. \textit{ERCC1} expression was analyzed by western blot in seventeen human gastric cancer cell lines, and all were found to express either 201, 202, and/or 203, but not 204 [31]. Although domain-specific functions that are clinically relevant to the 202 isoform of \textit{ERCC1} have been identified, there is a lack of structure-function data for the other isoforms with regard to cisplatin resistance. Considering this, we suggest that antibodies capable of detecting not only 202 but also other major \textit{ERCC1} isoforms may be useful for evaluation of cisplatin sensitivity. Therefore, we used 9D11, a novel antibody that recognizes \textit{ERCC1} isoforms 201, 202, and 203 [31]. We did not, however, identify a significant prognostic impact of \textit{ERCC1} protein expression when using this 9D11 antibody.
In conclusion, we believe that this is the first multi-omics study to evaluate the prognostic and predictive value of ERCC1 expression in patients with unresectable or recurrent gastric cancer. We demonstrate that genomic and transcriptomic analyses can guide the selection of cytotoxic chemotherapy and recommend that gene sequencing is performed before selecting patients for specific treatment regimens.

Declarations

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Authors’ contributions

Y. Yamada: Conceptualization, investigation, writing-original draft, data curation, formal analysis, editing, funding acquisition, and project administration. Investigation, writing-original draft, and editing. K. Nagashima: Data curation, formal analysis, and editing. M. Azuma: Investigation, data curation, and editing. M. Masutani: Investigation, data curation, and editing. H. Ichikawa: Investigation, data curation, formal analysis, and editing. S. Iwasa: Investigation and editing. N. Takahashi: Investigation and editing. H. Hirano: Investigation and editing. K. Kanato: Investigation and editing. N. Machida: Investigation and editing. T. Kinoshita: Investigation and editing. H. Hata: Investigation and editing. H. Kawakami: Investigation and editing. D. Takahari: Investigation and editing. N. Boku: Investigation and editing. Y. Kurokawa: Investigation and editing. M. Terashima: Investigation and editing. T. Yoshikawa: Investigation and editing. S. Sekine: Investigation and editing. N. Hiraoka: Investigation, data curation, and editing.

Competing interests

Y. Yamada has received lecture fee from Taiho Pharmaceutical. K. Nagashima has received consulting fee from Senju Pharmaceutical, Toray Industries, and Kowa. S. Iwasa is the employee of Chugai Pharma, and has received honoraria from Taiho Pharmaceutical, Lilly Japan, Chugai Pharma, Ono Pharmaceutical, Daiichi-Sankyo, Bristol-Myers Squibb Japan, and Agilent, institutional research funding from Daiichi-Sankyo, Bristol-Myers Squibb, Eisai, Merck Serono, Bayer, Ono Pharmaceutical, Astellas Pharma, Pfizer, Seagen, Zymeworks, Taiho Pharmaceutical, and AstraZeneca. N. Takahashi has received honoraria from Ono Pharmaceutical, Bristol-Myers Squibb Japan, and Taiho Pharmaceutical. H. Hirano has received honoraria Bristol-Myers Squibb Japan, Chugai Pharma, Novartis, Taiho Pharmaceutical, Fujifilm, and Teijin Pharma, and institutional research funding BeiGene. N. Machida has received honoraria from Taiho Pharmaceutical, Bristol-Myers Squibb Japan, Ono Pharmaceutical, Daiichi-Sankyo, Lilly Japan, Yakult Honsha, Takeda, MSD K.K, Chugai Pharma, Merck KGaA, Novartis, and Astellas Pharma, and institutional research funding from MSD, AstraZeneca, Amgen, Ono Pharmaceutical, Taiho Pharmaceutical, ALX Oncology, and Bristol-Myers Squibb Japan. T. Kinoshita has received lecture fees from Johnson & Johnson, Intuitive Surgical, Medtronic, Olympus Medical Systems, Daiichi Sankyo, Lilly Japan, Bristol-Myers Squibb Japan, Kaken Pharmaceutical, and Taiho Pharmaceutical. H. Kawakami has...
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References


Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures
Figure 1

Overall survival (OS) stratified by *ERCC1* mRNA expression and treatment arms

CS, cisplatin plus S-1; DCS, docetaxel with cisplatin plus S-1

Patients treated with DCS had longer OS than those with CS in high *ERCC1* mRNA expression (a) but low *ERCC1* (b).
Incidence of somatic mutation and survival in metastatic gastric cancer

a) TP53 mutation was most commonly observed mutation in gastric cancer. b) TP53 status had no impact on OS following treatment with either CS or DCS (HR, 1.02; 95% confidence interval, 0.69–1.51). c) Patients with wild type TP53 had better PFS than those with TP53 mutant (HR, 1.33; 95% confidence interval, 0.91–1.93). d) OS of patients segregated based on mutations of representative genes.

Supplementary Files

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