*Oncology Research*, Vol. 25, pp. 93–97
Printed in the USA. 

0965-0407/17 $90.00 + .00
DOI: https://doi.org/10.3727/096504016X14719078133564
E-ISSN 1555-3906
www.cognizantcommunication.com



# Identification of Sensitivity Predictors of Neoadjuvant Chemotherapy for the Treatment of Adenocarcinoma of Gastroesophageal Junction

Shoumiao Li,*† Baozhong Li,† Jiaxiang Wang,* Da Zhang,* Zhiqiang Liu,† Zhizhong Zhang,† Wei Zhang,† Yunjie Wang,† Dongxiao Bai,† Jianyun Guan,† and Yong Zhang†

*Department of Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China
†Department of Surgery, Anyang Tumor Hospital, Anyang, Henan, P.R. China

The identification of reliable predictors of chemotherapy sensitivity and early screening of adenocarcinoma of gastroesophageal junction (AGEJ) patients who are resistant to chemotherapy has become an important area of clinical and translational research. We aimed to investigate the predictive value of seven cancer-associated cellular proteins for neoadjuvant chemotherapy in AGEJ patients. Clinical data of 93 patients who received neoadjuvant chemotherapy for locally advanced AGEJ between June 2010 and December 2014 were reviewed. All patients were administered the combination regimen of S-1 and oxaliplatin (SOX). Expression of P-glycoprotein (P-gp), glutathione S-transferase-π (GST-π), topoisomerase II (topo II), multidrug resistance gene-associated protein (MRP), lung resistance-related protein (LRP), Ki-67, and p53 was determined by immunohistochemistry (IHC) in AGEJ tissues before neoadjuvant chemotherapy. Chemotherapeutic efficacy was evaluated according to RECIST 1.0 standards and histopathological results, and the relationship between the expression of the cellular proteins and chemotherapy efficacy was analyzed. The SOX regimen was associated with an overall response rate of 46.2%. The frequency of expression of the seven cancer-associated factors in the AGEJ tissues was as follows: P-gp, 64.5%; GST-π, 39.8%; topo II, 72.0%; MRP, 33.3%; LRP, 68.8%; Ki-67, 62.4%; and p53, 40.9%. Expression of Ki-67 ($p=0.003$) and p53 ($p=0.009$) was significantly correlated with chemotherapy sensitivity. Elevated Ki-67 expression and decreased p53 expression predict for SOX insensitivity in AGEJ, and the cellular expression of these respective proteins may provide a useful reference for designing individualized chemotherapy regimens for AGEJ patients in the future.

**Key words: Gastroesophageal junction neoplasm; Siewert II type; Neoadjuvant chemotherapy (NACH); Predictive factors; Chemosensitivity**

## INTRODUCTION

The incidence of adenocarcinoma of the gastroesophageal junction (AGEJ) has increased dramatically over the past few decades[1]. In 1998, Siewert and Stein[2] classified AGEJ, for the first time, into three different tumor types. Siewert I AEGJ is a type of esophageal adenocarcinoma, Siewert III is a type of proximal gastric adenocarcinoma, while Siewert II has a unique characteristic.

In China, over 80% of AGEJ cases are clinical stage III or beyond, making them a regional problem rather than a local problem. Surgery remains the mainstay of treatment for AGEJ patients, but the results remain unsatisfactory[3], which partly explains the increasing use of chemotherapy alone and/or in combination with radiation therapy in combined modality regimens along with surgical resection to improve patient outcomes.

The use of neoadjuvant chemotherapy (NACH) in AGEJ[4] has gained increasing attention, as this approach can reduce the extent of the disease, resulting in higher R0 surgical resection rates. However, it is clear that strategies are needed that predict the sensitivity of AGEJ to chemotherapy. An accurate prediction of the response to NACH will help clinicians select more effective treatment strategies according to the molecular biological characteristics of the tumor and thus reduce the primary resistance ratio and avoid unnecessary chemotherapy.

Chemotherapy is an important element of the systematic treatment of malignant tumors, while the main obstacle to effective chemotherapy is multidrug resistance (MDR). The S-1 and oxaliplatin (SOX) regimen is a first-line regimen for AGEJ chemotherapy. Ki-67 expression has been reported to correlate with tumor cell proliferation rate, and several studies have investigated the expression of Ki-67 as a NACH predictive marker for solid tumors[5]. In vitro studies have shown that p53 is required for the efficient activation of apoptosis, suggesting that

Address correspondence to Jiaxiang Wang, Department of Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, P.R. China. Tel:13938260010; E-mail: wjiaxiang2001@hotmail.com *or* Baozhong Li, Department of Surgery, Anyang Tumor Hospital, Anyang, Henan 455000, P.R. China. E-mail: libaozhong99@126.com

overexpression (mutant p53 protein positive) of p53 may enhance cellular resistance to chemotherapeutic agents[6]. In this retrospective study, we examined the expression of P-glycoprotein (P-gp), glutathione S-transferase-π (GST-π), topoisomerase II (topo II), multidrug resistance gene-associated protein (MRP), lung resistance-related protein (LRP), Ki-67, and p53 in AGEJ biopsy specimens before NACH to identify reliable predictors of chemotherapy sensitivity. The findings from this study may provide the basis for developing specific individualized treatments for AGEJ patients in the future.

## MATERIALS AND METHODS

### *Patient Selection*

This study included 93 patients (81 males and 12 females; age: 40–76 years, median age: 66.6 years) with advanced Siewert II type AGEJ who received NACH between June 2010 and December 2014 at the Anyang Tumor Hospital, Anyang, P.R. China. The clinical stages before treatment were cT3~4Nl~3M0. The diameters of the lesions were measured on contrast-enhanced CT images for TNM staging based on AJCC 2010[7]. The preoperative pathological types of the AGEJs were as follows: 83 cases were low to moderately differentiated adenocarcinomas, 3 cases were highly differentiated adenocarcinomas, 5 cases were mucosal adenocarcinomas, and 2 cases were signet ring cell carcinomas. The inclusion criteria were as follows: (1) pathological diagnosis of adenocarcinoma by endoscopic biopsy; (2) absence of distant metastasis; (3) contrast-enhanced CT showing local abdominal mass with infiltration into the full thickness of the stomach (T3 and T4) or regional lymph node enlargement; (4) ECOG scores between 0 and 2, and absence of serious comorbid illnesses, including heart, lung, liver, kidney, or other visceral dysfunction; (5) no history of other malignant tumors or radiation and chemotherapy; and (6) consent for preoperative chemotherapy and surgery. This study was approved by the institutional review board, and informed consent was obtained from each subject.

### *Neoadjuvant Chemotherapy*

All patients in this study received NACH with the SOX regimen[8]: oxaliplatin (130 mg/m$^2$) was intravenously injected for 2–3 h on day 1, and a capsule containing tegafur, gimeracil, and oteracil potassium (S-1) (40–60 mg bid) was administered orally from day 1 to day 14. This procedure was repeated every 3 weeks for two cycles. Adjuvant agents such as hexadecadrol, cimetidine, granisetron, and diphenhydramine were administered simultaneously to reduce potential adverse reactions. The curative effect was evaluated 2 weeks after the completion of the second course of treatment. A standard AGEJ radical operation (D2) was performed if no tumor progression was observed after comparing imaging results before and after NACH. Adjuvant chemotherapy was administered routinely after surgery.

### *Immunohistochemistry*

Immunohistochemical detection of cellular proteins was performed before the administration of NACH. Tissue specimens were fixed with 10% formaldehyde, paraffin embedded, and then cut into 4-μm-thick sections. Pathological types were identified by conventional H&E staining.

### *Reagents*

Mouse anti-human monoclonal antibodies {P-gp (C494), GST-π (353-10), topo II (Ki-S1), MRP [PA28(6)], LRP (5A6), Ki-67 (MAB-0129), p53 (DO-7)}, an avidin–biotin peroxidase system (SP-9701 kit), and positive control slides were purchased from the Fuzhou Maixin Biotechnology Company (Fuzhou, P.R. China).

Topo II[9], Ki-67[10], and p53[10] proteins are located in the nucleus; P-gp[11] and MRP[11] are located in the membrane and cytoplasm; and LRP[12] and GST-π[13] are located only in the cytoplasm. The appearance of thick brown–yellow particles was considered to indicate positivity. The presence of <50% positive cells suggested low gene expression, and these tissues were designated as negative (−), while tissues with ≥50% positive cells were designated as positive (+). The results were independently analyzed by two different pathologists.

### *Assessment of the Response to the Chemotherapy Regimen*

Gastroscopy or ultrasonic gastroscopy and abdominal contrast-enhanced 64-slice spiral CT were performed before and after NACH, respectively, to evaluate the curative effect of the treatment regimen. Postoperative pathological examinations were performed for the patients who underwent surgery. The response of the local primary lesion to NACH was judged according to the RECIST 1.0 standard[14]. The response was categorized as complete remission (CR), partial response (PR), stable disease (SD), and disease progression (PD). The NCI-CTC 3.0[15] adverse effect assessment was used to evaluate adverse reactions.

### *Statistical Analysis*

Data were analyzed using SASW version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The *t*-test was adopted for group measurement data. The enumeration data were compared using the chi-square test. Logistic multivariate regression and Spearman rank correlation analyses were used to evaluate the data. All values were two sided, and statistical significance was defined as $p < 0.05$.

## RESULTS

### *Pathological Features*

Forty-eight cases were of the well-differentiated type, and 45 cases were of the poorly differentiated type (including poorly differentiated adenocarcinoma, mucosal adenocarcinoma, signet ring cell carcinoma, undifferentiated carcinoma, and carcinoma simplex)[16]. Seven patients showed PD, and surgical resection was not undertaken. R0 surgical resection was performed in 86 patients; the age of 54 patients was <65 years, and the age of 32 patients was ≥65 years. There was no significant correlation between patient age or degree of tumor differentiation and chemotherapy efficacy ($p > 0.05$). The characteristics of these patients are shown in Table 1.

### *Response to Chemotherapy*

Ninety-three patients completed two cycles of the 3-week SOX NACH. The main side effects experienced by patients were nausea, vomiting, granulocytopenia, thrombocytopenia, and peripheral neuropathy, which were symptomatically relieved after treatment. No adverse reactions that are higher than grade 3 were observed. Seven patients showed PD but did not accept surgical treatment. The remaining 86 patients underwent the standard AGEJ radical surgical resection (D2) 4 weeks after the start of the last cycle of NACH. Postoperative complications included three cases with anastomotic bleeding and four cases with anastomotic fistula, all of which were treated with conservative treatment.

### *Responses to Neoadjuvant Chemotherapy and Pathological Findings*

The responses of the 86 surgically treated patients to NACH were as follows: 6 cases of CR (6.5%), 37 cases of PR (39.8%), and 43 cases of SD (46.2%). The overall RR (CR + PR) was 46.2%, and the overall disease control rate was 92.4%, which indicates a high sensitivity to the 3-week SOX chemotherapy regimen. Postoperative pathological results were as follows: six cases did not show any residual cancer cells, and all of these cases were low- to moderately differentiated adenocarcinomas or low-differentiated adenocarcinomas, and not accompanied by mucous adenocarcinoma or signet ring cell carcinoma. Five cases showed only scattered cancer cell clusters, and the pathological types were low- to moderately differentiated adenocarcinoma, moderately differentiated adenocarcinoma with papillary adenocarcinoma, low-differentiated adenocarcinoma, and moderately differentiated adenocarcinoma.

All resected tissue specimens were examined according to a standardized histopathological protocol, with the TNM stage evaluated according to the 2010 American Joint Committee on Cancer TNM staging criteria (seventh edition)[17]: 11 cases could not be staged (residual cancer cells were not found in 6 cases and 5 cases showed scattered cancer cells, but the T stage could not be determined), 30 cases were stage II, and 45 cases were stage III. Histopathological response was assessed by two independent and blinded pathologists using the criteria described by the Japanese Research Society for Gastric Cancer[18].

**Table 1.** Comparison of Clinicopathological Features

| Characteristic | Responder | Nonresponder | *p* Value |
|---|---|---|---|
| Age (years)* | 66.01 ± 9.31 | 67.05 ± 6.86 | 0.321 |
| Tumor size | | | 0.098 |
| <4.0 cm | 9 | 19 | |
| ≥4.0 cm | 33 | 32 | |
| Differentiation type | | | 0.778 |
| Highly differentiated | 21 | 27 | |
| Poorly differentiated | 21 | 24 | |
| Lymph node metastasis | | | 0.311 |
| Positive | 12 | 10 | |
| Negative | 30 | 41 | |
| Pathological stage | | | 0.077 |
| cII | 18 | 13 | |
| cIII | 24 | 38 | |

*Values are mean ± standard deviation (range).

### *Association Between Protein Expression and Chemotherapeutic Efficacy*

The protein expression showed no obvious correlation with age or the degree of differentiation ($p > 0.05$). The expression of seven proteins and the association of these proteins with chemotherapeutic efficacy in 93 cases of AGEJ are shown in Table 2. P-gp, GST-π, topo II, MRP, and LRP expression was detected in 60 (64.5%), 37 (39.8%), 67 (72.0%), 31 (33.3%), and 64 (68.8%), respectively, and there was no significant difference between the positivity rates in the CR + PR and the SD + PD groups ($p > 0.05$). Ki-67 expression was detected in 58 cases (62.4%), and the Ki-67$^+$ rate in the CR + PR group was significantly higher than that in the SD + PD group ($\chi^2 = 8.570$, $p = 0.003$). p53 expression was positive in 38 cases (40.9%), and the positivity rate in the CR + PR group was significantly lower than that in the SD + PD group ($\chi^2 = 6.821$, $p = 0.009$). The logistic multivariate regression analysis indicated that Ki-67 and p53 were independent factors affecting the efficacy of NACH for AGEJ (OR = 3.827, 95% CI = 1.457–10.053, $p = 0.006$; OR = 0.279, 95% CI = 0.109–0.716, $p = 0.008$). In the Spearman correlation analysis, Ki-67 expression was positively correlated ($r = 0.268$, $p = 0.021$), Ki-67 expression was positively correlated with topo II expression ($r = 0.405$, $p = 0.001$), and no significant association was found for the other cellular proteins.

**Table 2.** The Relationship Between Protein Expression and Chemotherapy Efficacy

| Protein | CR + PR | SD + PD | Chi-Square Value | *p* Value |
|---|---|---|---|---|
| P-gp | | | 0.834 | 0.361 |
| + | 25 (59.5%) | 35 (68.6%) | | |
| – | 17 (40.5%) | 16 (31.4%) | | |
| GST-π | | | 0.530 | 0.467 |
| + | 15 (35.7%) | 22 (43.1%) | | |
| – | 27 (64.3%) | 29 (56.9%) | | |
| Topo II | | | 0.645 | 0.419 |
| + | 32 (76.2%) | 35 (68.6%) | | |
| – | 10 (23.8%) | 16 (31.4%) | | |
| MRP | | | 0.782 | 0.377 |
| + | 12 (28.6%) | 19 (37.3%) | | |
| – | 30 (71.4%) | 32 (62.7%) | | |
| LRP | | | 1.705 | 0.192 |
| + | 26 (61.9%) | 38 (74.5%) | | |
| – | 16 (38.1%) | 13 (25.5%) | | |
| Ki-67 | | | 8.570 | 0.003 |
| + | 33 (78.6%) | 25 (49.0%) | | |
| – | 9 (21.4%) | 26 (51.0%) | | |
| p53 | | | 6.821 | 0.009 |
| + | 11 (26.2%) | 29 (56.9%) | | |
| – | 31 (73.8%) | 22 (43.1%) | | |

P-gp, P-glycoprotein; GST-π, glutathione S-transferase-π; topo II, topoisomerase II; MPR, multidrug resistance gene-associated protein; LRP, lung resistance-related protein; CR, complete remission; PR, partial remission; SD, stable disease; PD, disease progression.

## DISCUSSION

This study is retrospective in method. SOX chemotherapy was used as the neoadjuvant regimen for AGEJ, and it yielded an overall response rate of 46.2%, which was similar to that previously reported[19]. This neoadjuvant regimen successfully reduced the tumor stage, and it was well tolerated, with the main side effects being nausea, vomiting, granulocytopenia, thrombocytopenia, and peripheral neuropathy, all of which were easily managed. There was only a small number of postoperative complications with three cases of anastomotic bleeding and four cases of anastomotic fistula, all of which were managed by conservative treatment. These findings suggest that NACH is safe and that it does not lead to an increased incidence of postoperative complications and surgical risk. There was no obvious correlation between the chemotherapeutic efficacy and the age of the patients or the degree of differentiation of the tumors.

Chemotherapy is an important element in the systematic treatment of malignant tumors, while the main obstacle to effective chemotherapy is MDR. The SOX regimen is a first-line regimen for AGEJ chemotherapy. In contrast, expression of Ki-67 was found to be an independent predictor of chemotherapy sensitivity. In the present study, we classified IHC Ki-67 expression into two categories according to the percentage of Ki-67$^{++}$ cells: low (<50%) and high (≥50%). The clinical response rate (CR + PR) for tumors with high Ki-67 expression was significantly higher than that for tumors with low Ki-67 expression. These results were consistent with those previously obtained for gastric cancer[20]. In the present study, p53 expression was classified into two groups: low expression (negative or nuclear positivity in <50% of tumor cells) and high expression (nuclear positivity in ≥50% of tumor cells). High expression of p53 in pretreatment biopsy specimens was observed in 56.9% of nonresponders and in 26.2% of responders ($p = 0.02$). These results suggested that high expression of p53 may reflect overexpression of the mutant-type protein, leading to resistance against neoadjuvant SOX chemotherapy. The chemotherapy efficacy rate in p53$^{+}$ patients was significantly lower than that in p53$^{-}$ patients, which was similar to results previously obtained for gastric cancer[21].

A positive correlation was observed between Ki-67 expression and topo II expression ($r = 0.405$, $p = 0.001$), but not with p53 expression ($r = -0.090$, $p = 0.49$). Thus, p53 expression showed no relationship with P-gp expression; this result contradicted the results obtained for gastric cancer in a previous study[22], indicating a difference in molecular biological characteristics between AGEJ and distal gastric cancer.

Recent studies have shown that the downstaging effect of NACH in locally advanced AGEJ is associated with a reduced systemic relapse rate and an improvement in overall survival that is independent of prognostic factors[23]. Furthermore, patients who experienced downstaging of their primary tumor after NACH had survival comparable to that of patients with equivalent early stage tumors who did not require chemotherapy. Thus, tumor stage after NACH seems to be more important than initial stage at presentation in terms of assessing prognosis. Previous research results show that higher pathologic response rates are correlated with improvement of long-term outcomes.

In conclusion, Ki-67 and p53 expression was associated with sensitivity to NACH in AGEJ specimens; therefore, the expression of these two cellular proteins could be used as predictive factors for chemotherapy. Furthermore, expression of these proteins could be used to predict for recurrence-free survival or overall survival. One of the potential limitations of this study is the relatively small sample size. For this reason, it will be important to confirm our findings with future studies that include a larger sample size.

*ACKNOWLEDGMENT: The study was funded by the Henan Province Science and Technology Tackling Key Project (112102310121).*

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