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TIME SUBMITTED 17-JAN-2023 05:45PM
PAPER ID 95622179

Prognostic value of Claudin 18.2 expression in gastric adenocarcinoma

Kayikcioglu E *et al*. Claudin 18.2 expression in gastric adenocarcinoma

Abstract

BACKGROUND

Claudin 18.2 (CLDN 18.2) is a cell surface protein expressed by gastric cancer cells. The monoclonal antibody zolbetuximab binds CLDN 18.2-positive cancer cells and causes cancer cell death. A few studies researched the prognostic effect of CLDN 18.2 expression in metastatic gastric adenocarcinoma.

AIM

To identify the prognostic value of CLDN 18.2 expression in patients with metastatic gastric adenocarcinoma.

METHODS

This study was conducted with 65 patients over the age of 18 who were diagnosed with metastatic gastric adenocarcinoma. We investigated the effect of CLDN18.2 expression on clinicopathological characteristics (age, gender, histological grade, lauren classification, family history, metastatic site, HER2 expression) and prognosis for patients with metastatic gastric adenocarcinoma.

RESULTS

CLDN 18.2 expression was positive in 73.8% (48) of the patients. During the median 17.7-mo follow-up period, 89.2% (58) of the patients died. Median progression-free survival (PFS) and overall survival (OS) were 6 (95%CI; 1.6-10.4) and 12 (95%CI: 7.5-16.5) months. There was no statistically significant correlation between CLDN18.2 expression and clinicopathological characteristics of the patients. In univariate and multivariate Cox regression analysis, there was no correlation between clinicopathological characteristics of patients and PFS or OS.

CONCLUSION

CLDN 18.2 expression is quite high in patients with gastric adenocarcinoma, identifying the proportion of the patients in whom zolbetuximab is efficacious. There is no statistically significant correlation with clinicopathological characteristics and OS. CLDN 18.2 is not a prognostic marker in patients with gastric adenocarcinoma although it is predictive.

Key Words: Gastric adenocarcinoma; Claudin 18.2; Overall survival; Clinicopathological characteristics

Kayikcioglu E, Yüceer RO, Cetin B, Yüceer K, Karahan N. Prognostic value of Claudin 18.2 expression in gastric adenocarcinoma. *World J Gastrointest Oncol* 2023; In press

Core Tip: Zolbetuximab is a new antibody drug targeting the cell surface protein claudin 18.2 (CLDN 18.2) expressed by gastric cancer cells. CLDN 18.2 expression, identifying the patient population who are susceptible to zolbetuximab, is discordant in different studies. The present study aimed to research the expression ratio of CLDN and its prognostic value for overall survival in patients with gastric adenocarcinoma in a single center located in Turkey.

INTRODUCTION

Stomach cancer represents the third most common cause of cancer-related mortality globally, and caused 768793 deaths in 2020 (7.7% of all cancer deaths)[1]. Most people with stomach cancer in its early stages show no symptoms. The majority of patients (60%) receive diagnosis at the advanced stage following the emergence of symptoms[2]. In light of phase 2 and 3 studies from Europe, peri-operative chemotherapy (ChT) has become standard for patients with stage 2 and 3 gastric cancer, but the 5-year overall survival (OS) is still approximately 36%[3,4]. The prognosis for locally advanced, unresectable, or

metastatic gastric cancer is poor; in clinical trials evaluating the effectiveness of ChT, the median survival time is typically less than one year[5].

Claudin 18, a member of the cell surface protein claudin family, has two isoforms claudin 18.1 expressed in lung tissue, and claudin 18.2 (CLDN18.2) expressed specifically in gastric tissue. CLDN 18.2 is also expressed by gastric cancer cells, showing that it is not lost during malignant transformation[6]. The monoclonal antibody zolbetuximab binds CLDN18.2-positive cancer cells and causes cancer cell death by antibody-dependent cellular toxicity and complement-dependent cytotoxicity. In MONO phase 2a study of zolbetuximab as a single agent, CLDN18.2-positive patients with metastatic gastric and gastroesophageal junction (G/GEJ) adenocarcinoma received a minimum of one line of ChT and showed a 23% response rate[7]. The phase 2 FAST study of zolbetuximab plus ChT (epirubicin, oxaliplatin, capecitabine; EOX) *vs* ChT (EOX) showed superior OS and progression-free survival (PFS), defining CLDN18.2 as a new target for cancer therapy[8].

We investigated the effect of CLDN18.2 expression on clinicopathological characteristics and prognosis of patients with metastatic gastric adenocarcinoma undergoing ChT.

MATERIALS AND METHODS

Patients admitted to the medical oncology clinic of Suleyman Demirel University hospital between January 2013 and December 2021 with metastatic gastric adenocarcinoma were enrolled in this study. All cases were histopathologically confirmed according to the 5th edition of the World Health Organization (WHO) classification of digestive system tumours[9]. The Protocol for the Examination of Specimens from Patients with Cancers of the Stomach 2022 of the College of American Pathologists was used to identify histopathologic subtype, tumor location, tumor grade, and HER2 for gastric adenocarcinoma[10]. From the hospital database, the following clinical data were obtained; age, gender, histological type and grade, family history of gastric cancer, metastatic site, HER2 expression, PFS, and OS. The ethics committee of Suleyman Demirel University approved the study with date and number 01/04/2022-102. Patients

who accepted participation in the study, who were older than 18 years old, followed-up in the medical oncology clinic of Suleyman Demirel University hospital and whose paraffin blocks for diagnosis of gastric adenocarcinoma could be reached were enrolled in the study.

Immunohistochemistry

Hematoxylin and eosin (HE) sections representing the tumor of patients diagnosed with gastric adenocarcinoma were re-examined. The best paraffin block was selected for immunohistochemistry staining. Sections with 4-micron thickness were taken from paraffin blocks and transferred onto an adhesive coated slide system. The following method was used for immunohistochemical staining with streptavidin-biotin. Sections were incubated at 56 °C for 12 h for deparaffinization. Three percent hydrogen peroxide was used to block endogenous peroxidase. Antigen retrieval was performed in a microwave oven for 20 min using 0.01 mol/L Tris/EDTA buffer pH 9.0. Sections were coated with primary antibodies including CLDN 18.2 (rabbit monoclonal antibody, Clone EPR19202, at 1/500 dilution, Abcam, United Kingdom) and incubated at room temperature for 2 h. Sections were incubated for another 20 min at room temperature after the addition of binding (secondary) antibody (Goat Anti-Rabbit IgG H&L (HRP) kit, ABCAM, United Kingdom). The streptavidin-biotin complex was added. 3,3'-Diaminobenzidine was used as chromogen for visualization. CLDN 18.2 non-tumor gastric tissues were used as positive controls for each staining session.

Evaluation of immunohistochemical staining

Pathology slides were reviewed by two expert pathologists (ROY and NK) who did not know patient treatments and outcomes. Tumor cells were scored positive for CLDN 18.2 if they showed definite membranous staining and negative if tumor nuclei and cell membrane did not have immunoreactivity. Staining intensity was scored between 0 and 3 (absent: 0, weak: 1, moderate: 2, strong: 3).

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 26.0 (SPSS Inc., Chicago, IL, United States). Age and clinical characteristics were compared between patients with expression of CLDN 18.2 using the Mann-Whitney *U*-test for individual samples. In patient tumor samples with expression of CLDN 18.2, gender, localization, family history, Lauren classification, grade, sites of metastasis, liver and lung metastases, and history of adjuvant and neoadjuvant ChT were compared using Pearson's chi-square test. The correlation between CLDN 18.2 and HER2 was determined with the Spearman correlation test. OS and PFS were estimated using the Kaplan-Meier method, and a log-rank test was used to compare study groups in terms of survival. Multivariate analyses were performed using Cox regression analysis. A P value of < 0.05 was considered statistically significant.

RESULTS

Sixty-nine patients were screened and sixty-five were included in the study. The mean age was 64.6 years ± 12.9 years. Of patients, 49 (75.4%) were male and 16 (24.6%) were female. Table 1 shows the demographic and clinicopathologic characteristics of the patients according to CLDN 18.2 expression. Immunohistochemical staining was used to screen 65 metastatic gastric adenocarcinoma cases for the pathological significance of CLDN 18.2 expression (Figure 1). CLDN 18.2 expression was positive in 73.8% (48) of the patients.

During the median 17.7-mo follow-up period, 89.2% (58) of the patients died. Median PFS and OS were 6 mo (95%CI; 1.6-10.4) and 12 mo (95%CI: 7.5-16.5). There was no statistically significant correlation between CLDN18.2 expression and clinicopathological characteristics of the patients (Figure 2).

In univariate and multivariate Cox regression analysis for PFS, there was no correlation between clinicopathological characteristics of patients and PFS (Table 2).

In univariate and multivariate Cox regression analysis for OS, older age was an independent risk factor for poor OS (Table 3).

DISCUSSION

Gastric cancer is common and fatal. With targeted agents and immunotherapy, the median OS of patients with metastatic gastric cancer has reached 13.8-14.4 mo[11,12]. Novel therapies are critical for extending the survival of gastric adenocarcinoma patients. CLDN 18.2 is a tight junction molecule found on the surface of gastric mucosa epithelium and gastric cancer cells[6]. In metastatic gastric cancer patients, the monoclonal antibody zolbetuximab targeting CLDN 18.2 contributes to OS alone and when combined with ChT had tolerable side effects such as nausea and vomiting[7,8]. Worldwide clinical trials of zolbetuximab in the first-line setting, in combination with ChT and immunotherapy, are ongoing for G/GEJ adenocarcinoma (NCT03505320, NCT03504397, and NCT03653507). Histopathological subtype was diffuse in 36.9% (24) of patients and intestinal in 63.1% (41) and there was no correlation with CLDN 18.2 expression. In a study including 481 patients with gastric cancer, there was no correlation between histopathological subtype per Lauren classification and CLDN 18.2 expression, as in our study[13]. However, in a study including 263 Japanese patients with gastric adenocarcinoma, diffuse histopathological subtype was associated with strong CLDN 18.2 expression[14]. In another study of 85 patients with gastric adenocarcinoma, intestinal subtype was associated with strong CLDN 18.2 expression[15]. There was no correlation between grades of tumors and CLDN 18.2 expression in a study including 485 patients with esophageal adenocarcinoma[16]; however, grade 3 tumors were associated with strong CLDN 18.2 expression in two studies[13,14]. HER-2 expression was positive in 16.9% (11) of patients, and there was no correlation between HER-2 and CLDN 18.2 expression. In 3 different studies, there was no correlation between HER-2 and CLDN 18.2 expression[13,15,17], while there was an inverse correlation in a study including patients with esophageal adenocarcinoma[16]. In the present study, CLDN 18.2 expression was detected in 73.8% (48) of patients, with moderate to strong expression (≥ 2+) in 43.1% (*n* = 28). CLDN 18.2 expression was detected in 87%, with moderate and strong expression in 51.5%, of Japanese patients in a study conducted by Rohde *et al*[14], and moderate to

strong expression was present in 49% of patients with G/GEJ adenocarcinoma in the FAST study conducted by Sahin *et al*[6]. There was no correlation between clinicopathological characteristics of the patients and OS in the present study, consistent with other studies[13,15,16].

Inconsistent with the present study, in two studies by Türeci *et al*[7] and Sahin *et al*[8], CLDN 18.2 expression was detected only in 17.1% and 14.1%. This could be due to the different patient cohorts in the studies, as well as the different kits used to detect CLDN18.2 expression. Few studies were published in the literature until now regarding the expression of CLDN 18.2 in gastric adenocarcinoma. Conflicting results exist about the CLDN 18.2 expression ratios and the relationship between these parameters and the clinicopathological characteristics of patients with gastric adenocarcinoma; however, the studies are consistent that in showing there is no correlation between CLDN 18.2 expression and OS, as in the present study. The proportion of patients with gastric adenocarcinoma in whom zolbetuximab was efficacious was determined by the MONO and FAST trials. Our findings are consistent with these studies.

Our study's limitations include the relatively small number of patients analyzed and the retrospective character. Additional studies with a larger number of patients are needed to define the effect of CLDN 18.2 expression on OS.

CONCLUSION

CLDN 18.2 expression is quite high in patients with gastric adenocarcinoma, identifying the proportion of the patients in whom zolbetuximab is efficacious. There is no statistically significant correlation with clinicopathological characteristics and OS. CLDN 18.2 is not a prognostic marker in patients with gastric adenocarcinoma.

ARTICLE HIGHLIGHTS

Research background

Claudin 18.2 (CLDN 18.2) is a cell surface protein expressed by gastric cancer cells and a new target for the monoclonal antibody named zolbetuximab.

Research motivation

The question is whether CLDN 18.2 expression on gastric cancer cells is prognostic.

Research objectives

To identify the prognostic value of CLDN 18.2 expression in patients with metastatic gastric adenocarcinoma.

Research methods

We investigated the effect of CLDN18.2 expression on clinicopathological characteristics (age, gender, histological grade, lauren classification, family history, metastatic site, and HER2 expression) and prognosis for patients with metastatic gastric adenocarcinoma.

Research results

There was no statistically significant correlation between CLDN18.2 expression and clinicopathological characteristics of the patients. In univariate and multivariate Cox regression analysis, there was no correlation between clinicopathological characteristics of patients and progression-free survival or overall survival. The expression of CLDN 18.2 is predictive for zolbetuximab in metastatic gastric adenocarcinoma but it is not prognostic.

Research conclusions

CLDN 18.2 expression is high in metastatic gastric adenocarcinoma and predictive for zolbetuximab but it is not prognostic.

Research perspectives

Detection of new prognostic and predictive markers will make gastric cancer more manageable.

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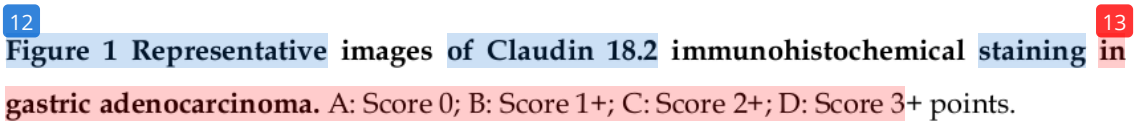

Figure 1 Representative images of Claudin 18.2 immunohistochemical staining in gastric adenocarcinoma. A: Score 0; B: Score 1+; C: Score 2+; D: Score 3+ points.

Figure 2 Kaplan-Meier curves for according to claudin 18.2 expression scores. A: Progression-free survival; B: Overall survival according to claudin 18.2 expression scores. CLDN 18.2: Claudin 18.2.

Table 1 Clinicopathological characteristics of patients with gastric adenocarcinoma based on claudin 18.2 expression

	Number of cases		CLDN18.2 score								*P* value
			0		1		2		3		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Age (yr)											
< 65	30	46.2	4	13.3	10	33.3	9	30.0	7	23.3	0.091
≥ 65	35	53.8	13	37.1	10	28.6	5	14.3	7	20.0	
Gender											
Male	49	75.4	14	28.60	15	30.60	11	22.40	9	18.40	0.314
Female	26	24.6	3	18.8	5	31.3	3	18.8	5	31.3	
Lauren classification											
Intestinal	41	63.1	9	22.00	12	29.30	10	24.40	10	24.40	0.221
Diffuse	24	39.9	8	33.3	8	33.3	4	16.7	4	16.7	
Tumor grade											
G1	30	46.2	9	30.0	8	26.7	7	23.3	6	20.0	0.889
G2	8	12.3	1	12.5	3	37.5	2	25.0	2	25.0	
G3	27	41.5	7	25.9	9	33.3	5	18.5	6	22.2	
Localization											
Cardia	18	27.7	3	16.70	9	50.00	3	16.70	3	16.7	0.307
Corpus	10	18.5	4	33.3	5	41.7	1	8.3	2	16.7	
Antrum	12	15.4	3	30.0	3	30.0	2	20.0	2	20.0	
Pylorus	2	2.1	0	0.0	0	0.0	2	100.0	0	0.0	
Antropyloric	23	35.4	7	30.4	3	13.0	6	26.1	7	30.4	
Her2Neu											
Negative	54	83.1	13	24.1	15	27.8	13	24.1	13	24.1	0.116
Positive	11	16.9	4	36.4	5	45.5	1	9.1	1	9.1	
Family history											
No	40	61.5	13	32.5	9	22.5	10	25.0	8	20.0	0.751

Yes	14	21.5	2	14.3	6	42.9	2	14.3	4	28.6	
Unknown	11	16.9	2	18.2	5	45.5	2	18.2	2	18.2	
Liver metastasis											
No	33	50.8	8	25.00	10	31.30	6	18.80	8	25.00	0.703
Yes	32	49.2	9	27.3	10	30.3	8	24.2	6	18.2	
Lung metastasis											
No	48	73.2	9	52.9	3	17.6	2	11.8	3	17.6	0.053
Yes	17	26.8	8	16.7	17	35.4	12	25.0	11	22.9	
Metastasis sites											
Liver	16	24.6	2	12.5	7	43.8	2	12.5	5	31.3	0.050
Lung	4	6.2	2	50.0	0	0.0	0	0.0	2	50.0	
Peritoneum	11	16.9	0	0.0	5	45.5	3	27.3	3	27.3	
LAP	14	21.5	4	28.60	2	14.30	6	42.90	2	14.30	
Brain	2	3.1	2	100.0	0	0.0	0	0.0	0	0.0	
Liver + Lung	17	26.2	7	41.2	6	35.0	2	11.8	2	11.8	
Ovary	1	1.5	0	0.0	0	0.0	1	100.0	0	0.0	
Adjuvant chemotherapy											
No	29	44.6	8	27.6	9	31.0	6	20.7	6	20.7	0.793
Yes	36	55.4	9	25.0	11	30.6	8	22.2	8	22.2	
Neoadjuvant chemotherapy											
No	61	91.8	14	23.0	20	32.8	13	21.3	14	23.0	0.097
Yes	4	8.2	3	75.0	0	0.0	1	25.0	0	0.0	
Exitus											
No	7	10.8	0	0.0	3	42.9	3	42.9	1	14.3	0.401
Yes	58	89.2	17	29.3	17	29.3	11	19.0	13	22.4	

CLDN18.2: Claudin 18.2; LAP: Lymphadenopathy.

Table 2 Univariate and multivariate analysis of baseline characteristics for progression-free survival

	Progression-free survival univariate analysis				Progression-free survival multivariate analysis		
	HR	95%CI	*P*		HR	95%CI	*P*
Age (yr)	1.36	0.80-2.30	0.26	Age (yr)	1.29	0.71-2.33	0.41
Gender	1.40	0.76-2.56	0.28	Gender	1.49	0.73-3.05	0.28
Lauren classification	0.89	0.52-1.53	0.67	Lauren classification	0.93	0.39-2.22	0.87
Tumor grade	0.85	0.49-1.47	0.56	Tumor grade	0.91	0.58-1.43	0.69
Family history	0.87	0.45-1.77	0.75	Family history	0.51	0.20-1.28	0.15
Liver metastasis	1.09	0.64-1.85	0.75	Liver metastasis	1.07	0.60-1.91	0.82
Lung metastasis	0.93	0.52-1.66	0.79	Lung metastasis	0.98	0.49-1.94	0.95
Localization	0.94	0.42-2.11	0.88	Localization	1.01	0.81-1.24	0.98
Metastasis sites	0.83	0.27-2.60	0.75	Metastasis sites	0.99	0.84-1.18	0.94
Her2Neu	0.81	0.40-1.64	0.56	Her2Neu	0.85	0.37-1.93	0.69
CLDN18.2	1.22	0.54-2.32	0.77	CLDN18.2	1.30	0.54-3.19	0.56

CLDN18.2: Claudin 18.2.

Table 3 Univariate and multivariate analysis of baseline characteristics for overall survival

	Overall survival univariate analysis	Overall survival multivariate analysis

	HR	95%CI	*P*		HR	95%CI	*P*
Age (yr)	2.46	1.39-4.33	0.01	Age (yr)	3.17	1.45-6.92	0.01
Gender	1.10	0.61-1.99	0.75	Gender	0.65	0.26-1.59	0.34
Lauren classification	1.28	0.66-1.94	0.66	Lauren classification	1.23	0.24-6.16	0.81
Tumor grade	0.41	0.15-1.07	0.07	Tumor grade	0.29	0.08-1.06	0.06
Family history	0.83	0.36-1.97	0.67	Family history	2.14	0.68-6.71	0.19
Liver metastasis	0.94	0.56-1.59	0.82	Liver metastasis	0.74	0.33-1.65	0.46
Lung metastasis	0.71	0.39-1.27	0.25	Lung metastasis	0.58	0.22-1.52	0.27
Localization	0.91	0.46-1.79	0.78	Localization	2.14	0.68-6.71	0.19
Metastasis sites	1.36	0.30-6.09	0.69	Metastasis sites	1.88	0.52-6.82	0.34
Her2Neu	1.11	0.56-2.22	0.77	Her2Neu	0.90	0.35-2.34	0.83
CLDN18.2	1.68	0.81-3.50	0.12	CLDN18.2	2.78	0.85-9.07	0.09

CLDN18.2: Claudin 18.2.

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