Original article:

Relatıonshıp between C-erb-B2 expressıon and other prognostıc factors in gastrıc cancer

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Abstract

Background: Gastric cancer-related deaths are among the leading causes of cancer-related deaths. Clinical trials with targeted agents continue in the treatment of stomach cancer, with randomized trials of chemotherapy to prolong survival in the treatment of metastatic gastric cancer. Metastatic stomach cancer treatment is also becoming increasingly personalized to the characteristics of the patient and tumor as it is in breast cancer. *Result:* Trastuzumab has shown randomized trial (TOGA study) in c-erbB2 positive metastatic stomach and gastroesophageal junction adenocancer patients to prolong median survival.Immunohistochemically, the presence of cerbB2 positivity and scoring at the time of diagnosis or in the resection material suggests that patients, especially in the metastatic stage, is necessary. The grade (score) of Cebb2 positivity was more pronounced in adenocarcinomas especially located anatomically close to the gastroesophageal junction. *Conclusion*: In our study, it was aimed to reveal the relationship between the demographic characteristics of patients who are candidates for treatment and the level of cerbB2 positivity and anatomic localization, especially in the metastatic stage if stomach and thyroid cancer are considered to be a common condition in our region.

Keywords: c-erbB2; Gastric cancer

Introduction:

Gastric cancer has an important place in deaths due to cancer.[1] Studies reported from the US and other western countries have reported a significant reduction in the incidence of gastric cancer over the last 60 years, but an increase over the last 15 years in newly diagnosed proximal gastric and gastroesophageal junction adenocarcinomas.[2] Gastric adenocarcinomas are genetic and epigenetic variations is a heterogeneous disease.[3] C-erb-B2 overexpression may also differ between gastric subtypes.[4] The human epidermal growth factor receptor 2 (HER2) gene locates on the long arm of the seventeenth chromosome (KR17);[5] Encodes the transmembrane receptor protein, which plays a role in intracellular tyrosine kinase activity in cell growth and proliferation, cell differentiation, apoptosis, adhesion, migration-like functions .[6-8] Also known as a transmembrane receptor protein C-erb-B2. [9] The overgrowth of Her2 has been described in the development of many cancers; Colon, bladder, ovary, endometrium, lung, uterus cervix, head & neck, esophagus and stomach cancer.[4,7,10]. Today, the most common uses of anti-HER2 antibodies are breast and stomach tumors.[11]

Gastric carcinoma is common in the eastern part of Turkey.[16] The aim of this study was to determine the sex, age, tumor localization, histological differentiation grade and stage, operable rates, cerbb2 frequency of 338 patients who were admitted to the

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Erzurum Regional Training and Research Hospital Medical Oncology outpatient clinic between January 2015 and January 2017 and to evaluate their interrelationships.

Patients and methods

The study consisted of 338 patients admitted to the Erzurum Regional Training and Research Hospital Medical Oncology outpatient clinic between January 2015-and January 2017, who had gastric adenocancer diagnosis in our hospital or another center. The information about the patients was obtained by retrospectively reviewing the computer automation system used in our hospital, hospital files of the patients and patient files in the oncology unit. Gender, age, localization of tumor, grade and stage of histologic differentiation, operable rates, frequency of CBR2, and interrelationships were evaluated in patients who concluded as adenocarcinoma.

Statistical Analysis

IBM SPSS Statistics version 18 computer program was used for statistical analysis. For the 95% confidence interval, 2-way p-values were used for all tests and the significance level of p-value was considered to be smaller than 5% (p <0.05). Student's t test, Mann Whitney U test, Chi-square, Fisher Exact, Pearson and Sperman correlation tests were used in the analyzes.

Ethical approval: The research was accepted by the ethics committee of Erzurum Region Training and Research Hospital, Internal Medicine Clinic, Erzurum.

Results

The average age of 334 patients participating in the study was 64.62.7% of the cases were male and 37.3% were female.29,9% of female patients had gastric adenocarcinom, 7,4% gastroesophageal junction adenocarcinom.49.1% of the male patients had gastric gastricadenocarcinom, 13.6%gastroesophageal junction adenocarcinom.79% of the group was gastric cancer and 21% of the group was gastroesophageal junction adenocarcinom.There was no significant difference in the incidence of gastric cancer among males and females. (Male: 62,7% n = 212, female: 37,3% n = 126, chi-square score: 0,68).65.3% of the cases were operable and 34.7% were inoperable. (table5) In the analysis performed, the operable ones were found to be significantly higher in the cardia and gastroesophageal junction tumors.(Chi-square: 0.013). The tumor was found in 61 cases (18.2%) corpus, 4 cases (1.2%) fundus, 103 cases (30,7%) in cardia, 80 cases (23,8%) in gastroesophageal complex, 41 cases In 19 cases (5.7%), it was found

to be localized in the comple gastric and in 28 cases (8,3%) in lesser curvature. There was no significant relationship between sex and localization in the analysis. (Chi-square score: 0.514.) (table1) In immunohistochemical examination; 147 patients had C-erb-B2 expression. There was no significant relationship between sex and Cerb b2 score in the analysis. (Male: 66,7% n = 147, female: 33,3% n = 49, chi-square score: 0,175).(table2)In gastroesophageal junction adenocarcinom.,cerb b2 positivity is significantly higher. (gastricadenocarcinom: 79,6% n = 117, gastroesophageal junction adenocarcinom: 20,4% n = 30, chi-square score: 0,045)There is no significant difference between histopathological types and cerb2scorus. In the analysis performed, signet ring cell type was found significantly more in women. (Fisher exact score: 0.04)(table 3- table 4)

According to Lauren's classification ;40 patients (11,9%) were intestinal type gastric adenocarcinomas, 294 patients (87,8%) were of diffuse type adenocarcinomas. Of 19 intestinal type adenocarciomas, 11 (7,5%) cases showed Her2/neu expression, whereas only 97 (66%) of 127 diffuse gastric carcinomas were found positive. The difference of C-erb-B2 overexpression rates between intestinal and diffuse type carcinomas wasnot statistically significant

When grouped according to stage; 7 patients (2,1%) were in stage I,29 patients (8,7%) were in stage II , 155 patients (46,3%) were instage III and 144 (43%) patients were in stage IV.There was no significant difference between histological type and stage. There is no significant difference between stage and cerb2 score.

Discussion

Althoughtheprevalence of gastricadenocarcinoma has decreased in thelastdecade; It is still the third mostcommoncause of cancerdeathafterlungcancerandliverworldwide[12]. The cancer records in Turkey are 2455 and the frequency of gastric cancer is 8.52% according to the Ministry of Health 2014 data.[13] The incidence of gastric cancer varies in different geographical regions. Gastric cancer is common in Turkey in the region of Erzurum.[14] In this study, we evaluated the data of 338 patients who were admitted to Erzurum regional education and research hospital Medical Oncology outpatient clinic between January 2015 and January 2017.

Theincidence of stomachcancer in males is morethanfemales[17]Themale / femaleratio of thecasegroup in our study was 1,6 / 1 (62,7% male,

Table1: Association between sex and tumor localizationCrosstabulation

			corpus	fundus	cardia	gastroesophageal junction	antrum	Comple gastric	lesser curvature	Total
sex	female	Count	21	3	39	30	16	4	12	125
		% of Total	6,3%	0,9%	11,6%	8,9%	4,8%	1,2%	3,6%	37,2%
	male	Count	40	1	64	50	25	15	16	211
		% of Total	11,9%	0,3%	19,0%	14,9%	7,4%	4,5%	4,8%	62,8%
Total		Count	61	4	103	80	41	19	28	336
		% of Total	18,2%	1,2%	30,7%	23,8%	12,2%	5,7%	8,3%	100,0%

Table2: Association between c-erbB2 expression and sex Crosstabulation

			cerb2 negative	cerb2 positive	Total
sex	female	Count	15	34	49
		% of Total	10,2%	23,1%	33,3%
	male	Count	23	75	98
		% of Total	15,6%	51,0%	66,7%
Total		Count	38	109	147
		% of Total	25,9%	74,1%	100,0%

Table3 Association between c-erbB2 expression and diagnosis

			0	1	2	3	Total
Diognosis	Gastric adenocarsinom	Count	36	33	31	17	117
		% of Total	24,5%	22,4%	21,1%	11,6%	79,6%
	gastroesophageal junction adenocarcinom	Count	2	10	10	8	30
		% of Total	1,4%	6,8%	6,8%	5,4%	20,4%
Total		Count	38	43	41	25	147
		% of Total	25,9%	29,3%	27,9%	17,0%	100,0%

Table4: Association between c-erbB2 expression anddiagnosis Crosstab

			cerb2 negative	cerb2 positive	Total
diognosis	Gastric adenocarsinom	Count	36	81	117
		% of Total	24,5%	55,1%	79,6%
	gastroesophageal junction adenocarcinom	Count	2	28	30
		% of Total	1,4%	19,0%	20,4%
Total		Count	38	109	147
		% of Total	25,9%	74,1%	100,0%

Table5: Association between localization and operation history Crosstab

			Operation history		Total
			Non-operabl	operabl	
Tumor localization	corpus	Count	34	27	61
		% of Total	10,1%	8,1%	18,2%
	fundus	Count	1	3	4
		% of Total	0,3%	0,9%	1,2%
	cardia	Count	71	32	103
		% of Total	21,2%	9,6%	30,7%
	gastroesophageal junction	Count	63	16	79
		% of Total	18,8%	4,8%	23,6%
	antrum	Count	23	18	41
		% of Total	6,9%	5,4%	12,2%
	Comple gastric	Count	10	9	19
		% of Total	3,0%	2,7%	5,7%
	lesser curvature	Count	18	10	28
		% of Total	5,4%	3,0%	8,4%
Total		Count	220	115	335
		% of Total	65,7%	34,3%	100,0%

37,3% female).Ourresultsweresimilartodata of TURKEY.Despite a decliningtrend in the incidence of gastric cancer in recent years, it is reported that there is an increase in proximallocalized gastric cancer.[18] Proximal tumors have worse prognosis than distal tumors because of their larger size, increasing frequency, deeper invasion and lymph node metastasis more frequent. In our study, proximal stomach cancer was detected in 54.5% of our cases and distal gastric cancer incidence was found to be 45,5.9%.

The TNM staging system is an extremely important and guiding system of staging stomach cancer staging, prognosis determination and shaping of treatment. Parameters such as the depth of invasion of the tumour (T), local lymph node metastasis (N) and distant metastasis (M) are used in TNM staging. The studies show that patients in the same pathological stage may have different prognosis. Many biological reagents are observed in order to determine these different prognostic groups.[19,20]

Surgical, chemotherapy and radiotherapy treatment options for gastric cancer may be combined. The only potential treatment for gastric cancer is surgery. In our study,65.3% of the cases were operable and 34.7% were inoperable. In the analysis performed, the operable ones were found to be significantly higher in the cardia and gastroesophageal junction tumors.(Chi-square: 0.013).

Determination of prognostic factors in gastric cancer has an important role in estimating the survival of the patients and determining the treatment method.[21]Targeted therapy in gastric cancer treatment has begun to use the increasing value of trastuzumab (EGFR antibody) with ToGa study, also included in the guideline of NCCN2013[22]. HER2 over expression and/or amplification might be a molecular abnormality linked to the development of gastric cancer.[23]Upregulation of matrixmetalloproteinasesby c-erbB2 can alsoresult in an increasedinvasiveness, a strongerangiogenicresponse, and a higherapoptosisresistance[24] In our study, only 146 patients were found to have HER2 receptor status. Tanner et al. Identified HER2 amplification in 12% of 131 cases of gastric adenocarcinoma and 24% of 100 cases with gastroesophageal junction tumor.[25] In our study, In gastroesophageal junction adenocarcinom., cerb b2 positivity is significantly higher. (gastricadenocarcinom: 79,6% n = 117, gastroesophageal junction adenocarcinom: 20,4% n = 30, chi-square score: 0,045)In the widest range of study on HER2 expression, 3883 patients with

advanced stage gastric cancer were evaluated and HER2 positivity was found as 22.9%.[26] In this study, In gastroesophageal junction tumors, HER2 positivity was identified at a higher rate than the gastric tumors. (23,8% n:80)

Conclusion: All these results suggest that C-erbB-2 has been reported in the literature a prognostic factor independent of other factors .These data can make some contribution towards improving the prediction of the efficacy of trastuzumab-based therapy in gastric cancer

Conflict of interest: Authors declare no conflict of interest.

Authors' Contributions:

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