Original Article

Clinicopathological Features of Young Gastric Cancer and New Inflammatory Prognostic Markers

Genç Mide Kanserinin Klinikopatolojik Özellikleri ve Yeni İnflamatuar Prognostik Belirteçler

Ahmet Gülmez[1], Mustafa Dikilitaş[2]

[1]Adana City Education and Research Hospital, Department of Medical Oncology
[2]Inonu University Faculty of Medicine. Department of Medical Oncology. Malatya

ABSTRACT

Introduction: This study aimed to evaluate the clinicopathologic features of young gastric cancer (GC) patients and to investigate the factors affecting survival (OS).

Materials and methods: In this study, the data of 55 patients diagnosed under the age of 40 were obtained by retrospective evaluation of hospital records. Clinicopathological features and some laboratory parameters of this patient group and new inflammatory prognostic markers (IPM) obtained from these parameters were evaluated.

Results: The mean age of the patients in this study was 33 years. The majority of the patients were male. Patients were evaluated according to human C-erbB2 positivity too. The identified patients as positive were only 7% of all patients. Also, the patients were evaluated for platinum sensitivity too. It was found that 30% of the patients were sensitive to platinum treatments. Also, survival times of the patients were evaluated with IPM. Neutrophil-lymphocyte ratio (NLR), mean platelet volume/platelet count, C-reactive protein/albumin ratios were calculated separately. Survival results were analyzed based on the mean values of all 3 prognostic markers. Even though there was a significant numerical difference, no statistical significance was found.

Discussion: This study was conducted to examine the clinicopathological features and survival time of young GC patients. Low C-erbB2 positivity and high platinum resistance were found among this patient population. In addition, inflammatory prognostic markers, which were found to be associated with survival in most cancers, were found to cause significant numerical differences in terms of survival in our study.

Keywords: Young Gastric Cancer, Prognosis, Novel Prognostic Markers

ÖZET

Giriş: Bu çalışma genç mide kanseri (GC) hastalarının clinicopathologic özelliklerini değerlendirmek ve sağ kalıma (OS) etki eden faktörleri araştırmayı amaçladı.

Gereç ve yöntemler: Bu çalışmada, hastane kayıtlarının retrospektif olarak değerlendirilmesi ile 40 yaş altı tanı almış 55 hastanın verileri elde edilmiştir. Bu hasta grubunun klinikopatolojik özellikleri ve bazı laboratuvar parametreleri ile bu parametrelerden elde edilen yeni inflamatuar prognostik belirteçler (IPM) değerlendirildi.

Bulgular: Çalışmamızda hastaların ortalama yaşı 33'tü. Erkek hastaların sayısı çoğunluktaydı. Hastalar C-erbB2 pozitifliğine göre de değerlendirildi. Pozitif olarak saptanan hastalar, tüm hastaların sadece %7'siydi. Hastalar aynı zamanda platin duyarlılığı açısından da değerlendirildi. Hastaların %30'unun platin tedavilerine karşı duyarlı olarak saptandı. Hastaların SK süreleri inflamatuar prognostik belirteçler eşliğinde de değerlendirildi. Nötrofil-lenfosit oranı (NLR), ortalama platelet volümü/platelet sayısı (MPV/platelet sayısı), C-reaktif protein/albümin oranları (CAR) ayrı ayrı hesaplandı. Her 3 prognostik belirtecin de ortalama değerleri baz alınarak SK sonuçları incelendi. Bu değerler ve SK arasında rakamsal olarak belirgin farklılık olmasına rağmen istatistiksel bir anlamlılık saptanmadı.

Tartışma: Bu çalışma genç mide kanseri hastalarının klinikopatolojik özelliklerini ve SK sürelerini

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incelemek için yapılmıştır. Çalışmamız sonucunda bu hasta grubunda düşük C-erbB2 pozitiflik oranı ve yüksek platin direnci olduğu saptanmıştır. Ayrıca çoğu kanserde sağkalımla ilişkili olduğu saptanan inflamatuar prognostik belirteçlerin, çalışmamızda da SK açısından belirgin rakamsal farklılık oluşturduğu görülmüştür.

Anahtar kelimeler: Genç Mide Kanseri, Prognoz, Yeni Prognostik Belirteçler

Introduction

Gastric cancer (GC) is an important cancer worldwide. It is estimated that there will be more than 1,000,000 new cases and 783,000 deaths for GC in 2018. This makes GC the fifth most frequently diagnosed cancer worldwide and the third most common cause of cancer death [1]. Gastric cancer shows a marked variation for age at diagnosis. Gastric cancer is usually detected more frequently in older people in the United States, and the average age at diagnosis is 68. More than 95% of all newly diagnosed GC patients are over the age of 40 [2]. According to literature, patients under the age of 40 are referred to as young GC. Although few patients with young GC are seen in the literature, young GC patients have started to be seen more frequently in recent years. This situation can be caused by many different reasons. In addition to the development of cancer screenings and diagnostic procedures, the fact that people come into contact with carcinogens from an earlier age can be counted among the reasons for this situation.

Young adult patients with GC face unique challenges such as tumor biodiversity, differences in treatment efficacy, tolerance and compliance with treatment, fertility preservation, and psychosocial considerations associated with premature death [3-4]. There are some variation in the specific threshold used to define young adult GC patients. Large study groups, such as the National Cancer Institute [5], used age 39 as the upper limit to define young adult GC. Diffuse type GC is more common in this group of young adults. These patients are diagnosed later than elderly patients and have a more aggressive tumor biology [6].

In this study that we have completed, we evaluated the clinico-pathological features, treatments they received, and responses to these treatments in patients aged 40 years and younger. In addition, we aimed to evaluate some laboratory parameters, progression-free survival (PFS) and overall survival (OS) data of these patients.

Materials and Methods

In this study, we retrospectively evaluated GC patients who were diagnosed pathologically in our hospital between 2010 and 2020. When the hospital records were examined, it was seen that the number of young adult GC patients diagnosed between these years was 55. Gender, ECOG (Eastern Cooperative Oncology Group) performance status, predominant complaint at the time of diagnosis, diagnosis method, TNM stage at the time of diagnosis [7], surgical procedure and surgical technique, treatment modalities, hemoglobin (Hb), neutrophil (Neu) of the patients in our study, lymphocyte (Lym), platelet (Plt), albumin (Alb), total protein (Tp), C-reactive protein (CRP) results were obtained from hospital records. NLR was calculated as absolute neutrophil count / absolute lymphocyte count. MPR was calculated as mean platelet volume/absolute platelet count. CAR; It was calculated by taking the ratio of CRP to albumin. If patients receiving chemotherapy received platinum-based therapy, the platinum sensitivity of these patients was also evaluated. Treatment response assessment in metastatic patients was performed according to the Criteria for Evaluation of Response in Solid Tumors (RECIST) version 1.1 using magnetic resonance imaging (MRI), computed tomography (CT), or Positron Emission Tomography (PET/CT) at 6-8 week intervals. Patients who received adjuvant therapy were included in the follow-up after the end of the targeted treatment period. This study has ethics committee approval dated 29.09.2020 and numbered 2020-979. All procedures

performed in studies involving human participants comply with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and later amendments or comparable ethical standards.

Statistical Analysis

Clinicopathological features were evaluated. Overall survival (OS) was calculated as the time from diagnosis to death from any cause. Overall survival was assessed using the Kaplan Meier method and compared using log-rank tests. Statistical analyzes were performed with IBM SPSS Statistics for Windows (version 22.0. Armonk, NY). A p value less than 0.05 was considered statistically significant. Patient survival was determined as mean ± standard deviation and was written in months.

Results

In this study, a total of 55 patients were evaluated in accordance with the inclusion and exclusion criteria. The patients were evaluated according to the complaint of predominance at the time of admission to the hospital. The predominant complaint was abdominal pain in 36 (65%) patients, and nausea and vomiting in 12 (27%) patients. Less common causes were weight loss in 5 (9%) patients and admission to the hospital with bleeding symptoms in two (4%) patients. When evaluated as a diagnosis method; 49 (89%) of the patients were diagnosed by endoscopy, while six (11%) patients were diagnosed by surgery. Patients were evaluated for differentiation from biopsy or postoperative pathology reports. Of the patients, five (9%) patients were diagnosed as well differentiated, seven (13%) patients moderately differentiated, 11 (20%) patients poorly differentiated, 18 (33%) patients with signet ring cell, and 14 (25%) patients with poorly cohesive carcinoma. The patients were also evaluated in terms of cerbB2 as a result of staining with immuno-histochemical evaluation. 37 (67%) of these patients were found to be cerbB2 negative. It was evaluated as +1 positive in 10 (19%) of the patients, +2 positive in four (7%) and +3 positive in four (7%) patients. The clinical and demographic data of these patients are shown in Table-1. The total number of patients who were considered locally advanced and operated for curative purposes was 35 (64%). On the other hand, the number of patients who were metastatic at the time of diagnosis was 20 (36%). When the patients were evaluated as surgical and non-surgical, it was seen that 40 (73%) patients were operated and 15 (27%) were not operated. While 35 of these operated patients were operated for curative purposes as previously stated, 5 patients were operated for palliative purposes. Subtotal gastrectomy was performed in 26 (65%) of 40 patients who underwent surgery, while total gastrectomy was performed in 14 (35%) patients. When the patients are classified according to the type of chemotherapy they receive; It was seen that five (9%) patients received neoadjuvant

Table 1. Demographic Data and Clinicopathological Characteristics of the Patients

	Number of Patients (n=55)	(%)
Age		
Median Age	33	
Range	(18-40)	
Gender		
Male	31	56
Female	24	44
ECOG		
0	15	27
1	21	38
2	19	35
Dominant Complaint		
Abdominal Pain	36	65
Nausea and Vomiting	12	22
Weight Loss	5	9
Bleeding	2	4
Diagnostic Method		
Endoscopy	49	89
Surgery	6	11
Subtype-Differential		
Well Differentiated	5	9
Poor Differentiated	7	13
Middle Differential	11	20
Ring Cell	18	33
Poorly Cohesive	14	25
CerbB2		
Negative	37	67
+1	10	19
+2	4	7
+3	4	7
Stage at Diagnosis		
Stage II	5	9
Stage III	30	55
Stage IV	20	36

Table 2. Surgical Characteristics and Treatments of the Patients

	Number of Patients (n 55)	(%)
Indication of Surgery		
Curative Approach	35	64
Palliative Approach	5	9
No Surgery	15	27
Type of Surgery		
Subtotal Gastrectomy	26	65
Total Gastrectomy	14	35
Lymph Node Dissection		
D1	4	10
D2	31	77
Unknown	5	13
Chemotherapy Reason		
Neoadjuvant	5	9
Adjuvant	27	49
Palliative	16	29
Could not get	5	9
No indication	2	4
Chemotherapy Type		
FUFA	11	23
FOLFOX	22	46
DCF	10	21
FLOT	3	6
EOX	2	4
Chemoradiotherapy	18	37,5
Completing Systemic Treatment	30	62,5
Platinum Sensitivity	11	30

FUFA: Fluorouracil/Folinic Acid, FOLFOX: Oxaliplatin Plus İnfusional 5-FU And Leucovorin, DCF: Docetaxel, Cisplatin and Fluorouracil, FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel, EOX: Epirubicin, Oxaliplatin, And Capecitabine

chemotherapy, 27 (49%) patients received adjuvant chemotherapy, and 16 (29%) patients received palliative chemotherapy. Although five (9%) patients had indication for treatment, they could not receive treatment due to poor performance status, and two (4%) patients had no indication for treatment. The patients were also evaluated according to the type of chemotherapy. 11 (23%) patients were treated with FUFA, 22 (46%) patients with FOLFOX, 10 (21%) patients with DCF, three (6%) patients with FLOT, and two (4%) patients with EOX. The patients were also evaluated according to the planned systemic treatment completion status. While 30 (62.5%) of 48 patients who started systemic treatment completed the planned treatment period, it was observed that the planned treatment period could not be reached in 18 (37.5) patients. The data from 37 patients treated with platinum agents were also re-evaluated for platinum sensitivity. The times determined for platinum sensitivity; at least 6 months after the end of treatment for metastatic disease, and 12 months after the end of treatment for patients who received adjuvant or neoadjuvant therapy. When evaluated with these criteria, a total of 11 (30%) patients were found to be platinum sensitive. The operation information of the patients and the systemic treatments of their received are shown in Table-2.

Some laboratory parameters of the patients were also evaluated. Patients were evaluated as neutrophil-lymphocyte ratio (NLR). The mean value was determined as 5.60 (0.99-21.20). The mean value for the evaluation of MPV/Platelet ratio, another inflammatory prognostic marker, was found to be 0.049 (0.011-0.450). Similarly, the mean ratio of CRP/Albumin, an inflammatory prognostic marker, was 1.38 (0.016-7.42). The relationship between inflammatory prognostic markers and OS is shown in Table 3.

Discussion

Gastric cancer patients are usually diagnosed over the age of 40. However, the frequency of GC patients under the age of 40 has been increasing in recent years, especially in western societies. And these patients are mostly diagnosed in the 30-39 age range [8]. In a previously published article, it was shown that young GC patients were diagnosed at a more advanced stage and their survival was worse [9]. The reasons for this poor prognosis are controversial. Some authors argue that GC diagnosed at an early age has genetic origins and therefore has a more aggressive course. According to another view, in many countries of the world, especially in countries where GC is endemic, young patients cannot be detected early due to inadequate screening programs and therefore the prognosis of these patients is worse. Possibly, both hypotheses may account for the poor course of these patients.

Table 3. Inflammatory Prognostic Markers and Survival Times

	Overall Survival-Month (OS)	Min	Max	p value
		%95 CI		
NLR				
<5,6 (n 18)	12,44±7,40	8,92	15,6	p>0,05
>5,6 (n 14)	7,08±4,72	5,11	9,27	
MPV/Platelet				
<0,049 (n=26)	9,73±7,20	7,02	12,78	p>0,05
>0,049 (n=6)	11,66±5,15	5,10	9,15	
CRP/albumin				
<1,38	11,18±4,93	8,95	13,38	p>0,05
>1,38	8,70±6,71	3,48	5,92	

NLR: Neutrophil-Lymphocyte Ratio, MPV: Mean Platelet Volume, CRP: C-Reactive Protein

Young GC has not been clearly defined yet. In previous studies, there are studies based on the age of 50, 40, and 34 years [10]. This definition of young GC varies due to the development level and life expectancy of the countries. In this study, we classified patients aged 40 years and younger as young GC. The mean age of the patients in this study was 33 years. More than half of the patients were male patients. In a previous study, the fact that GC seen at a young age was more common in women was attributed to hormonal changes. In addition, it has been stated that the reason for the excess of male cancer detected at advanced age is exposure to carcinogens more than women [10]. However, there is no clear cause and effect relationship related to this situation. Because the number of male patients was found to be higher in different series studies performed on young GC patients. In the same study, diffuse histology and poorly differentiated tumors were observed to be more common in younger patients. However, no difference was found regarding the diagnosis of younger patients at a later or more advanced stage. In addition, it has been observed that young GC patients have a shorter DFS period [10].

In another study, almost 5000 patients were evaluated and patients younger than 40 years of age were classified as young GC. There were 136 patients in this group. In this study, no difference in OS was found between younger patients and older patients. However, it has been reported that the performance status of young patients is better than that of elderly patients, and the complication rates after surgery are lower than those of the elderly. In addition to this situation, as in previous studies, pathologically worse differentiated tumors were found to be more common in younger patients. In addition, in this study, it was observed that the frequency of lymph node metastasis in young patients was higher than in patients over 40 years of age [11]. The reason why both OS and DFS durations were not different from patients aged >40 years in this study may be that the systemic treatments they received were more potent due to the better performance status of the younger patients. Another meta-analysis involving young GC patients was published in 2020. According to this study, the clinicopathologic features of GC patients diagnosed under the age of 40 were evaluated in 19 different studies between 2010 and 2019. In the light of these studies, the rate of female patients, the rate of diffuse type GC, the rate of poorly differentiated GC, and the rate of diagnosis at a more advanced stage were found to be higher in younger GC patients [12].

The standard treatment for Her-2 positive advanced GC is a combination of trastuzumab and platinum-based chemotherapy. The study that made this treatment standardized is the

ToGA study [13]. As mentioned in this study, Her-2 amplification or over-expression varies between 7-34%. However, Her-2 positivity rate was found to be only 7% in this study. This low Her-2 positivity rate also reduces the treatment options that can be used in young GC patients. Unfortunately, in this study that we have completed, the number of patients who can use the Her-2 targeted therapy option is extremely low.

Recently, treatment options without the use of conventional chemotherapy have been developed for some types of cancer. However, in treatment-naive and especially platinum-sensitive GC patients, a systemic treatment plan cannot be made without the use of platinum-based chemotherapy. However, platinum resistance in some patients renders these treatments ineffective. Many studies investigating which patients have resistance to these treatments have been reported in the literature [14,15]. In this study, approximately 70% of the patients had platinum resistance. Such a high level of platinum resistance in young GC patients may explain the poor prognosis of the patients. Investigation of the causes of platinum resistance in young GC patients; It should be the main subject of future studies both for genomic polymorphisms that can explain the pathogenesis of the disease and to aim to increase the extremely poor survival of the disease.

Due to both platinum resistance and low rate of Her-2 positivity, the treatment options available in young GC patients are decreasing. At this stage, immunotherapy treatments, which have gained importance in recent years, can be considered as an option. There is no clear biomarker for immunotherapy yet. Previous studies have shown that immunotherapies are beneficial in patients with high microsatellite instability (MSI-H), regardless of tumor type. With this demonstrated clinical benefit, pembrolizumab treatment has been approved by the American Food and Drug Administration (FDA) in patients with MSI-H [16]. However, according to a previous meta-analysis, there is a lower rate of MSI-H/dMMR in early young GC patients than in advanced age GC patients [17]. All these situations prove that young GC patients are more difficult patients and that more research is needed in this area.

Inflammatory prognostic markers are especially important in predicting the prognosis of the disease. Recently, it has been studied in almost all cancer types. As a result of studies supporting each other, they have become important parameters used in clinical practice. These parameters have also recently been studied in GC. It was evaluated in one study in patients with stage III GC, which included a total of 225 patients. C-reactive protein/albumin ratio (CAR) and platelet lymphocyte ratio (PLR) were found to be independent markers that affect overall survival [18].

There is also a meta-analysis result in patients with GC. The data from 41 studies published between 2007 and 2020 were analyzed [19]. According to this meta-analysis, which included a total of 18,348 patients, the increased NLR value was confirmed to be a negative prognostic marker for OS. Certain cut-off values were used for the inflammatory prognostic markers mentioned in these studies. These cut-off values were determined based on the average value of the patients in some studies, a target value was determined in some studies, and Roc Curve analysis was performed in some studies. However, the number of patients should be sufficient for Roc curve analysis. In this study, which we completed, the mean values of the patients were calculated due to the small number of patients and this mean value was taken as the cut-off value. A significant numerical difference was found in all three inflammatory prognostic markers in overall survival calculated with these values. However, this numerical difference was not statistically significant due to the insufficient number of patients.

The shortcomings of our study are the small number of patients, data from a single center, and being a retrospective study. The strengths of our study are that there are very few young

GC studies in the world. Another strength is that it is the first study to evaluate all three inflammatory prognostic markers in young GC patients. It is important to confirm with larger patient numbers. Considering all these data, early-stage GC is an important problem that should be emphasized. In this patient group, new treatment options are needed because of the poor biological behaviour of the disease and less use of targeted therapy agents.

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Corresponding author e-mail: doktor.ahmetgulmez@gmail.com

Orcid ID:
Ahmet Gülmez 0000-0002-3353-344X
Mustafa Dikilitaş 0000-0002-3763-7529

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