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ORIGINAL ARTICLE

Gastric adenocarcinoma with neuroendocrine differentiation: Clinicopathological features and efficacy of modified DCF chemotherapy

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Summary

Purpose: *The aim of this study was to investigate the clinicopathological characteristics of patients with gastric carcinoma with neuroendocrine differentiation (NEDGC) and the efficacy of the modified DCF (mDCF) chemotherapy regimen.*

Methods: *Patients with NEDGC and non-NEDGC (pure adenocarcinoma) were evaluated comparatively in terms of pathological parameters, clinical parameters and treatment efficacy. Patients received treatment with mDCF (docetaxel, cisplatin and 5-fluorouracil).*

Results: *In total, 391 patients (35 with NEDGC and 356 with non-NEDGC) were included in this study. In particular, in the NEDGC group, the presence of lymphovascular invasion (LVI), presence of perineural invasion (PNI), median tumor size, and metastasis at the time of diagnosis were significantly higher than in the non-NEDGC group. mDCF was used as first-line chemotherapy regimen in 16 patients in the NEDGC group, and in 151 patients in the non-NEDGC group. In NEDGC and non-NEDGC groups overall disease control rate was 87.5% [partial response (PR) (50.0%), stable disease (SD) (37.5%)] and 80.8% [complete response (CR) (2.6%), PR (38.4%), SD (39.8%)], respectively. In the advanced-stage patients who had first-line mDCF, the median overall survival (OS) was 10.6 months (95% CI: 5.9-15.4) and 12.2 months (95% CI: 10.3-14.2) in NEDGC and non-NEDGC groups, respectively (p=0.88). The median progression-free survival (PFS) in the NEDGC and the non-NEDGC groups were 7.6 months (95% CI: 5.5-9.7) and 7.5 months (95% confidence interval/CI: 6.8-8.1), respectively (p=0.82).*

Conclusion: *NEDGC patients usually have higher LVI and PNI rates, and they present with advanced disease. In this group of patients, mDCF regimen may be an effective treatment option. However this statement needs to be verified by further prospective and multi-centered studies including a larger patient cohort.*

Key words: *gastric cancer, modified DCF, neuroendocrine differentiation, prognosis*

Introduction

Gastric epithelial tumors composed of exocrine and neuroendocrine cells may be divided into two main groups, as pure and typical endocrine tumors. Pure endocrine tumors are adenocarcinomas with interspersed neuroendocrine cells whereas typical endocrine tumors are mixed exocrine-neuroendocrine tumors in which the neuroendocrine component represents half or at least one third of the tumor tissue [1-3].

In 2010, the classification of neuroendocrine tumors was revised in the 4th edition of World Health Organization's (WHO) digestive tumor classification. Gastrointestinal and pancreatic neuroendocrine tumors were classified into following categories: mixed adenoneuroendocrine carcinoma (MANEC), neuroendocrine carcinoma (NEC), and neuroendocrine tumors (NET) [1]. Gastric carcinoma with neuroendocrine differentiation

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(NEDGC) has been defined as a gastric neoplasm containing both adenocarcinoma and neuroendocrine components within the same tumor tissue. In those tumors, differentiated neuroendocrine cells are scattered as single cells or cell clusters among gastric carcinoma cells. NEDGC is not included in the neuroendocrine tumors, and it is classified as an adenocarcinoma [1].

Adenocarcinomas originating from gastric tissue may sometimes possess a neuroendocrine differentiation. Although the true incidence of NEDGC is yet unknown, a few histopathological studies reported its incidence as 18.7-53% [4,5]. This wide range of incidence may be due to geographical, regional or racial variations, and may particularly be related to use of different diagnostic markers and standards [4,5].

Histological differentiation of gastric cancer has a strong correlation with the prognosis. More specifically, the grade of tumor cell differentiation correlates with aggressiveness of the neoplasm [6-9]. On the other hand, the correlation of neuroendocrine differentiation with prognosis it is not clear. Few studies, mostly histopathological articles, have investigated the prognostic value of neuroendocrine differentiation [10]. Clinical features or the therapeutic approaches of NEDGC were rarely mentioned in those papers. Currently, NEDGC are treated similar to other gastric adenocarcinomas, and there are no specific guidelines or treatment recommendations for this tumor type. Therefore, in this study we aimed to investigate the clinicopathological characteristics, and the efficacy of mDCF chemotherapy regimen in patients with NEDGC.

Methods

Patients diagnosed with gastric cancer in our hospital between September 2008 and March 2015 were retrospectively analyzed. A total of 391 patients with histopathologically proven gastric carcinoma were included in this study. The patients were divided into NEDGC and non-NEDGC groups. NEDGC was defined as the presence of differentiated neuroendocrine cells scattered as single cells or cell clusters among the gastric carcinoma cells, and positive staining of these cells with synaptophysin and chromogranin. Patients with classical neuroendocrine tumors or neuroendocrine carcinoma were excluded from the study.

Demographic and clinical parameters such as gender, age, weight loss, performance status as well as histopathological parameters such as diameter of the tumor, invasion depth to the gastric wall, disease stage, LVI and PNI were analyzed. In addition, the surgical method, adjuvant chemotherapy and radiotherapy, palliative chemotherapy, the response to the treatment, and survival data were also noted and analyzed. mDCF has been the preferred first-line chemotherapeutic regimen in patients with advanced-stage gastric cancer in our clinic after it was reported to be effective in metastatic gastric cancer cases in previous studies [11-13]. The mDCF regimen was administered as follows: docetaxel 60 mg/m^2/day (iv. day 1), cisplatin 60 mg/m^2/day (iv. day 1), and 5-fluorouracil 600 mg/m2/day (continuous infusion, days 1-5), every 3 weeks. The efficacy of mDCF as first-line chemotherapeutic regimen was analyzed by comparing the two groups. The response to chemotherapy was assessed using RECIST 1.1 criteria.

Staging of tumor was done according to the American Joint Committee on Cancer (AJCC) staging system (6th Edn) [14]. The performance status at the time of diagnosis was determined using the Eastern Cooperative Oncology Group (ECOG) system. Toxicity of treatment was determined based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

The health statuses of the patients were determined from the hospital health records, and the Central Population Administration System of the Turkish Republic registration system.

Statistics

The Statistical Package for The Social Sciences (SPSS), version 18.0 for Windows (SPSS, Inc, Chicago, IL, USA) software program was used for statistical analysis. $P<0.05$ was considered as statistically significant. Categorical variables were analysed using x^2 or Fihser's exact test. Survival analysis was performed with Kaplan-Meier method whereas log-rank test was used to compare differences between subgroups. OS of the patients receiving mDCF chemotherapy was defined as the interval between the initiation of chemotherapy and death or last follow-up date of the patient. OS was defined as the interval between diagnosis and death or last follow-up date for all patients included in the study. PFS was defined as the interval between the beginning of chemotherapy and disease recurrence or the date of last follow-up visit.

Results

Clinicopathologic characteristics

NEDGC patients (n=35) comprised 8.9% of all gastric adenocarcioma patients (n=391) and their clinicopathological features are shown in Table 1. The median age of all the study population was 58 years (range 22-88), 25.8% of the patients were females and 74.2% males. Of the whole 74.4% had ECOG performance status scores 0-1 at the time of diagnosis. Endoscopic examination findings revealed that 84.9% of the patients (n=332) had Borrmann type 3-4 tumors, with the primary tumor localized mostly at the cardia of the stomach (36.3%). Almost half of the patients had LVI

and PNI (52 and 49%, respectively). At the time of diagnosis, 48% of the patients had metastatic disease, liver and distant abdominal lymph nodes being the most common sites of metastasis (55.9 and 39.8%, respectively).

The patients with NEDGC and non-NEDGC were compared for their clinicopathological characteristics. Although the two groups did not show any significant differences for age, gender, comorbidities, smoking history, weight loss, Lauren classification, Borrmann type, or tumor localization, they showed some histopathological and clinical differences. LVI (NEDGC vs non-NEDGC: 82.9 vs 59.2%, p=0.007), and PNI (77.1 vs 56.4%, p=0.01) were more frequent in the NEDGC group. In addition, median tumor size was significantly larger (5 vs 4 cm, p=0.04), the patients with ECOG ≥2 were significantly more (45.7 vs 23.6%, p=0.004), and metastasis at the time of diagnosis was significantly more frequent (65.7 vs 45.8%, p=0.02) in the NEDGC group compared to the non-NEDGC group. On the other hand, the ratio of patients who had curative surgery was higher in the non-NEDGC group (34.3 vs 54.2%, p=0.02). Although not statistically significant, the NEDGC group had higher invasion depth (T3+T4 tumors), and a higher rate of liver metastasis with a trend for statistical significance (Table 1).

Table 1. Clinicopathological characteristics of the patients

Characteristics	*NEDGC (%) n=35*	*Non-NEDGC (%) n=356*	*Total n=391*	*p value*
Age (median, range)	59 (40-80)	58 (22-88)	58 (22-88)	0.83
Gender				
Female	8 (22.9)	93 (26.1)	101 (25.8)	
Male	27 (77.1)	263 (73.9)	290 (74.2)	0.67
Smoking	22 (62.9)	225 (63.2)	247 (63.2)	0.96
ECOG PS				
0-1	19 (54.3)	272 (76.4)	291 (74.4)	
2-4	16 (45.7)	84 (23.6)	100 (25.6)	0.004
Weight loss	17 (48.6)	155 (43.5)	172 (44.0)	0.56
Comorbidity	13 (37.1)	161 (45.2)	174 (44.5)	0.35
Lauren classification				
Intestinal	15 (50.0)	121 (46.2)	136 (46.6)	
Diffuse	14 (46.7)	135 (51.5)	149 (51.0)	0.84
Mixed	1 (3.3)	6 (2.3)	7 (2.4)	
Depth of invasion				
T1+T2	2 (6.7)	46 (20.3)	48 (18.7)	
T3+T4	28 (93.3)	181 (79.7)	209 (81.3)	0.07
Tumor size, cm (median, range)	5 (1.5-13)	4 (4-17)	4 (4-17)	0.04
TNM stage				
1-2	6 (17.1)	87 (24.4)	93 (23.8)	
3	6 (17.1)	106 (29.8)	112 (28.6)	
4	23 (65.8)	163 (45.8)	186 (47.6)	0.07
Borrmann type				
I+II	8 (22.9)	51 (14.3)	59 (15.1)	
III+IV	27 (77.1)	305 (85.7)	332 (84.9)	0.17
Tumor location				
Fundus-Cardia-Diffuse	8 (22.9)	134 (37.6)	142 (36.3)	
Corpus	11 (31.4)	113 (31.7)	124 (31.7)	
Antrum	16 (45.7)	109 (30.7)	125 (32.0)	0.12
LVI	29 (82.9)	173 (59.2)	202 (51.7)	0.007
PNI	27 (77.1)	164 (56.4)	191 (48.8)	0.01
Metastasis (at diagnosis)				
Yes	23 (65.7)	163 (45.8)	186 (47.6)	
No	12 (34.3)	193 (54.2)	205 (52.4)	0.02
Location of metastasis at diagnosis				
Liver	14 (40.0)	90 (25.3)	104 (55.9)	0.06
Peritoneum	3 (8.6)	52 (14.6)	55 (29.6)	0.32
Intra-abdominal distant LAP	9 (25.7)	65 (18.3)	74 (39.8)	0.28
Lung	4 (11.4)	18 (5.1)	22 (11.8)	0.11
Bone	2 (5.7)	15 (4.2)	17 (9.1)	0.67
Others	6 (17.1)	42 (11.8)	48 (25.8)	0.35

For abbreviations see text

No significant differences concerning the kind of treatment was noticed, and the two groups did not show any significant difference in terms of adjuvant chemotherapy/ chemoradiotherapy in patients who underwent curative surgery (p=0.70). First-line chemotherapy was administered to 23 patients in the NEDGC group, and to 193 patients in the non-NEDGC group. mDCF was used as the first line chemotherapy regimen in 16 (69.6%) patients in the NEDGC group, and in 151 (78.2%) patients in non-NEDGC group (Table 2). Among the patients who recieved mDCF therapy as first-line treatment in the NEDGC group, 8 (50%) showed PR, 6 (37.5%) SD and 2 (12.5%) had disease progression (PD). On the other hand, 4 (2.6%) had CR, 58 (38.4%) had PR, 60 (39.8%) had SD, and 29 (19.2%) patients had PD in the non-NEDGC group treated with mDCF (Table 3).

Analysis grade 3-4 hematological toxicities in the NEDGC patients revealed that 2 (12.5%) patients had anemia, 1 (6.2%) had thrombocytopenia, and 1 (6.2%) had neutropenia. In the non-NEDGC group, 21 (13.9%) patients had anemia, and 9 (5.9%) neutropenia. None of the patients in the NEDGC group had febrile neutropenia whereas in the non-NEDGC group febrile neutropenia occurred in 3.3% (n=5) of the patients who were hospitalized. Analysis of grade 3-4 non-hematological side effects in the NEDGC group revealed nausea and vomiting in 2 (12.5%) patients, and diarrhea in 1 (6.2%). In the non-NEDGC group, 8 (5.9%) patients had nausea-vomiting and 5 (3.3%) had diarrhea.

Table 2. Treatment characteristics of the patients with NEDGC and non-NEDGC

Characteristics	*NEDGC (%) n=35*	*Non-NEDGC (%) n=356*	*p value*
Curative surgery			0.02
Yes	12 (34.3)	193 (54.2)	
No	23 (65.7)	163 (45.8)	
Adjuvant CRT/RT			0.70
Yes	10 (83.3)	148 (76.7)	
No	2 (16.7)	45 (23.3)	
First-line chemotherapy			0.72
DCF	16 (69.6)	151 (78.2)	
Infusional FUFA	4 (17.4)	24 (12.4)	
CFF	3 (13.0)	18 (9.4)	
Second line chemotherapy			0.81
EOX	3 (60)	60 (67.4)	
FOLFIRI	1 (20)	17 (19.1)	
Capecitabine	1 (20)	12 (13.5)	

CFF: cisplatin/5 fluorouracil/folinic acid),CRT: chemoradiotherapy, DCF: docetaxel/ cisplatin/5 fluorouracil, EOX: epirubicin/oxaliplatin/ capecitabine, FUFA: 5 fluorouracil/folinic acid, FOLFIRI: 5 fluorouracil/ folinic acid/irinotecan, RT: radiotherapy

Table 3. Response to first-line mDCF

Response	*NEDGC (%) n=16 n (%)*	*Non-NEDGC (%) n=151 n (%)*
Complete response	-	4 (2.6)
Partial response	8 (50.0)	58 (38.4)
Stable disease	6 (37.5)	60 (39.8)
Progressive disease	2 (12.5)	29 (19.2)

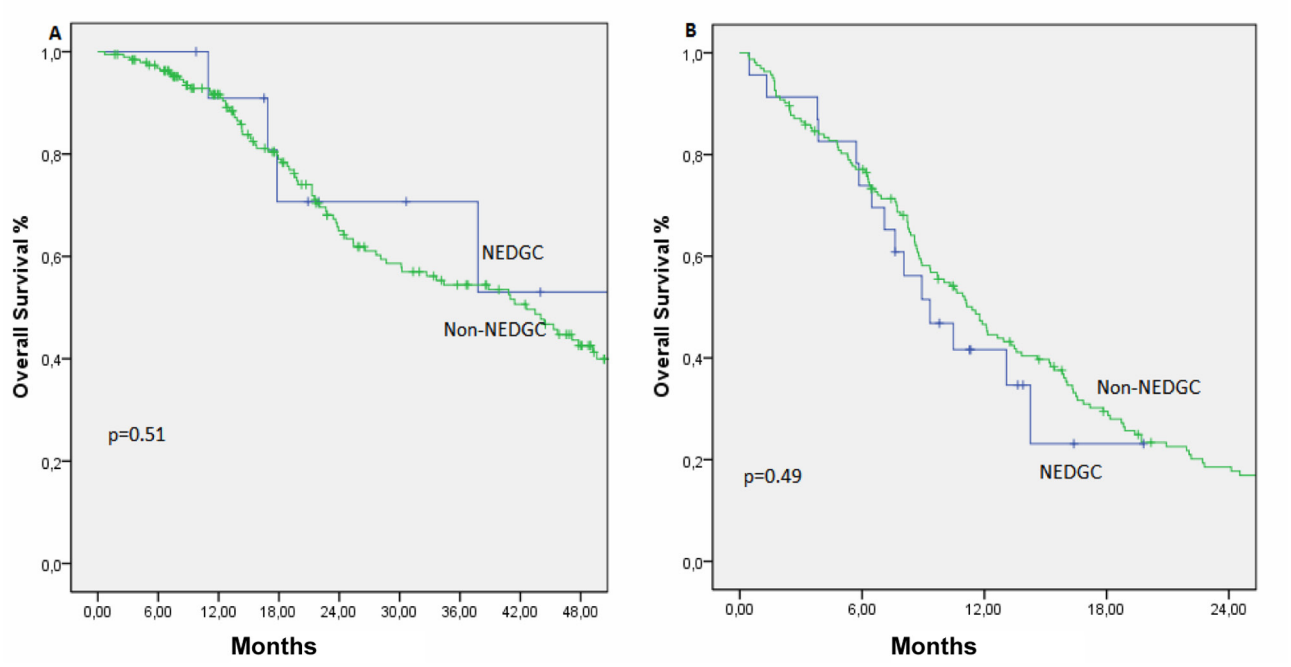

Figure 1. A) Univariate analysis for overall survival in stage I-III NEDGC and non-NEDGC patients; **B)** Univariate analysis for overall survival in stage IV NEDGC and non-NEDGC patients.

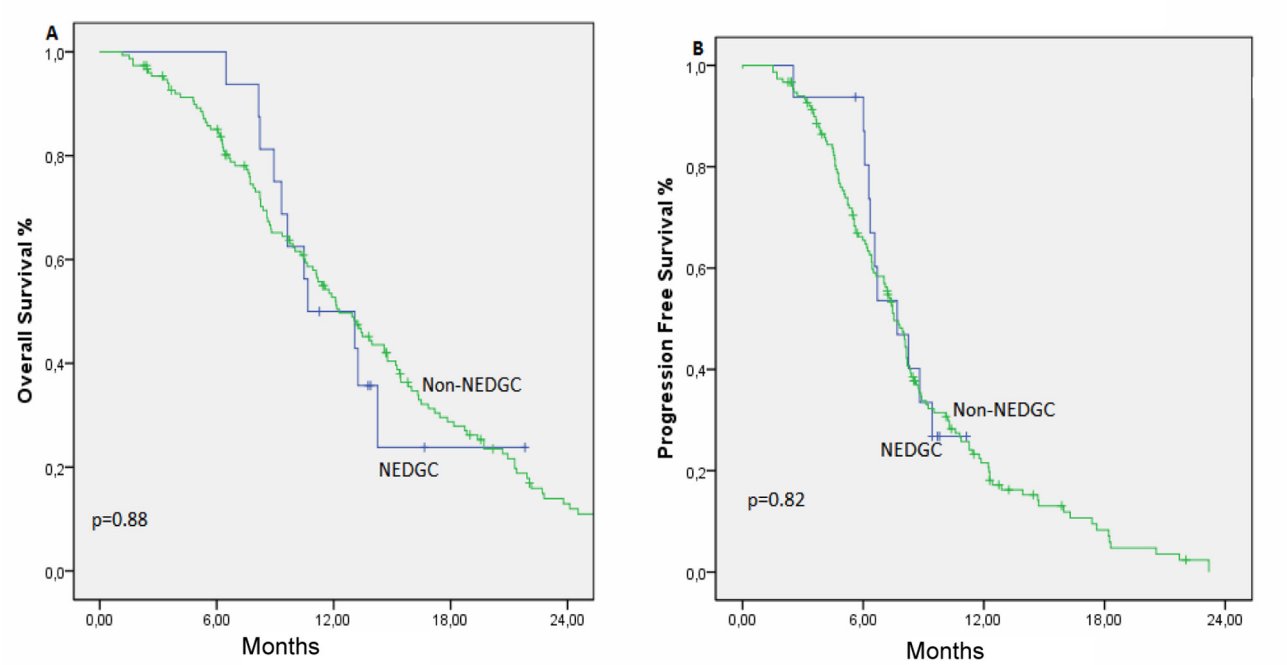

Figure 2. A) Univariate analysis for overall survival in NEDGC and non-NEDGC patients that were administered modified DCF. **B)** Univariate analysis for progression free survival in NEDGC and non-NEDGC patients that were administered modified DCF.

Survival

The median follow-up period of the NEDGC and non-NEDGC groups were 11.2 (range 0.46-69.2) and 15.2 months (range 0.43-83.0), respectively. The median OS was 16.8 months (95% CI 10.8-22.9) in the NEDGC group, and 20.9 months (95% CI 18.3-23.4) in the non-NEDGC group (p=0.59). When the patients were divided into stages I-III (non-metastatic) and stage IV (metastatic), OS was not significantly different in the NEDGC and non-NEDGC groups (p=0.51 and p=0.49, respectively) (Figure 1). In the advanced-stage patients who had first-line mDCF, the median OS was 10.6 (95% CI 5.9-15.4) and 12.2 months (95% CI 10.3-14.2) in the NEDGC and non-NEDGC groups, respectively (p=0.88). The median PFS in the NEDGC and non-NEDGC groups were 7.6 (95% CI 5.5-9.7) and 7.5 months (95% CI 6.8-8.1), respectively (p=0.82) (Figure 2).

Discussion

Gastric cancer constitutes 6.8% of all cancers worldwide, it is the fifth most frequent cancer, and the third most common cause of cancer-related deaths with a mortality rate of 8.8% [15]. Despite advancements of diagnostic and therapeutic modalities, it is still hard to say that the survival rates have improved significantly over time. It is essential to identify pathological subtypes in order to set up new treatment strategies, and eventually to increase survival.

It has been well known for a long time that there are neuroendocrine cells in the gastric mucosa which they give rise to tumors. Neuroendocrine cells scattered among typical gastric adenocarcinoma cells give rise to a particular pattern of gastric malignancy, known as NEDGC. Although a number of studies focused on neuroendocrine tumors, only a few studies investigated the clinicopathologic features or the therapeutic approaches of NEDGC. There are no sufficient data to determine the exact incidence of NEDGC among other histological subtypes of gastric adenocarcinoma. In our study, we found that NEDGC constituted 8.9% of all gastric adenocarcinomas.

The importance of some clinical and prognostic factors, namely LVI, PNI, and the disease stage, has been proven in gastric cancer [16,17]. In our study, we showed that some clinicopathological characteristics including LVI, PNI, and presence of metastasis at the time of diagnosis were significantly more frequent in the NEDGC group when compared to the non-NEDGC group. Previously, Kim et al. reported that stage 3 disease was the most common (45%) among 29 NEDGC patients who underwent gastrectomy alone, and the rates of LVI and PNI were higher in the NEDGC group (83% and 59%, respectively) [18]. In Zhang et al. [10] and Eren et al. [19] studies, stage 3-4 disease was reported in 70% and 63% of NEDGC patients, respectively. Consistent with the previous studies on NED-adenocarcinoma of other tissues such as prostate and endometrium [20,21], we found that the patients with NEDGC usually presented with

an advanced-stage cancer, and they had poor prognostic characteristics more often.

Several studies reported metastasis in 16-32% of gastric adenocarcinoma patients at the time of diagnosis, and the most common sites of metastasis were peritoneum, liver, and distant lymph nodes, in rank order [22,23]. In our study, metastasis at the time of diagnosis was more common in the NEDGC group (66%) compared to the non-NEDGC group (46%) (p=0.02), and these rates were higher than the ones reported in previous studies on gastric adenocarcinoma. By contrast with non-NEDGC patients and the previous reports, NEDGC patients had a higher tendency for liver metastasis and a lower tendency for peritoneal involvement. This finding may suggest that NEDGC is more likely to make hematogeneous metastasis and it does not directly invade the peritoneum. However, further multicenter studies with larger patient numbers are needed to further clarify this subject.

The standard therapy for metastatic gastric carcinoma is palliative chemotherapy. Single-drug regimens have achieved 6.7 months median OS while the median for combination treatment is 8.3 months [24]. In a phase III V325 study by Van Cutsem et al., it was reported that adding docetaxel to cisplatin/5-fluorouracil (CF) regimen improved not only the OS, but also the time to progression (TTP) parameter (TTP: 3.7 vs 5.6 months, OS: 8.6 vs 9.2 months; p<0.001, p=0.02, respectively) [25]. Since toxicity and febrile neutropenia were more common in standard DCF, mDCF regimen was started to be used [11-13]. The rates of overall disease control were reported between 64.9% and 90% in advanced-stage gastric cancer cases treated with mDCF [11,12]. Those studies reported neutropenia and anemia as the most common grade 3-4 hematological toxicities (4-8.1 and 5-11%, respectively), while grade 3-4 nausea, vomiting and diarrhea were observed in 5-15% of the patients as the non-hematological toxicities. Febrile neutropenia rate was reported as 2-5% [11,12,26]. In the present study, the overall disease control rate was 87.5%, with acceptable hematological and non-hematological toxicity, and febrile neutropenia rates in the NEDGC patients. The rates we reported are in concordance with the previous studies, and those seen in non-NEDGC patients. Although our study sample is quite small, it is still important since it is the first study to report the efficacy of chemotherapy in NEDGC patients. In advanced-stage NEDGC patients, mDCF may be considered as a treatment option with relatively favorable toxicity profile and high response rates.

The median OS has been reported as 8.7-10.7 months, and the median PFS as 6.2-7.4 months in studies focusing on patients with advanced-stage gastric cancer who were administered mDCF regimen [11-13,26,27]. Similar to previous studies, we reported OS and PFS in the NEDGC and non-NEDGC patients as 10.6 and 12.2, and 7.6 and 7.5 months, respectively (p=0.88 and p=0.82, respectively).

Our study has several limitations. First, it is a retrospective study, and the patients included had heterogeneous characteristics (advanced and early stages of the disease). Due to the retrospective study design we could not perform a comprehensive toxicity analysis. Despite our small sample size, the present study may contribute to the research of new therapeutic approaches for this particular histological subtype of gastric cancer, and this may lead to higher OS and PFS rates.

In conclusion, NEDGC patients usually have higher LVI and PNI rates, and they present with advanced disease. In this group of patients, mDCF regimen may be an effective treatment option, however this statement needs to be verified by further prospective and multi-centered studies including larger patient cohorts.

Conflict of interests

The authors declare no confict of interests.

References

1. Rindi G, Arnold R, Bosman FT. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND et al. (Eds): WHO classification of tumors of the digestive system. Lyon: IARC, 2010.
2. Lewin K. Carcinoid tumors and the mixed (composite) glandular-endocrine cell carcinomas. Am J Surg Pathol 1987;11:71-86.
3. Ooi A, Hayashi H, Katsuda S et al. Gastric carcinoma cells with endocrine differentiation show no evidence of proliferation. Hum Pathol 1992;23:736-741.
4. Ooi A, Mai M, Ogino T et al. Endocrine differentiation of gastric adenocar¬cinoma. The prevalence as evaluated by immu¬noreactive chromogranin A and its biologic significance. Cancer 1988;62:1096-1104.
5. Qvigstad G, Sandvik AK, Brenna E et al. Detection of

chromogranin A in human gastric adenocarcinoma using a sensi¬tive immunohistochemical technique. Histochemistry 2000;32:551-556.

6. Park JM, Jang YJ, Kim JH et al. Gastric cancer histology: clinicopathologic characteristics and prognostic value. J Surg Oncol 2008;98:520-525.
7. Wanebo HJ, Kennedy BJ, Chmiel J et al. Cancer of the stomach. A patient care study by the American College of Surgeons. Ann Surg 1993;218:583-592.
8. Sim YK, Kim CY, Jeong YJ et al. Changes of the clinicopathological characteristics and survival rates of gastric cancer with gastrectomy: 1990s vs early 2000s. J Korean Gastric Cancer Assoc 2009;9:200-206.
9. Seo WH, Seo BJ, Yu HJ et al. Analysis of prognostic factors in 1,435 surgically treated patients with gastric cancer. J Korean Gastric Cancer Assoc 2009;9:143-151.
10. Zhang T, Su D, Mao Z et al. Prognostic role of neuroendocrine cell differentiation in human gastric carcinoma. Int J Clin Exp Med 2015;8:7837-7842.
11. Keskin S, Yıldız I, Sen F et al. Modified DCF (mDCF) regimen seems to be as effective as original DCF in advanced gastric cancer (AGC). Clin Transl Oncol 2013;15:403-408.
12. Ozdemir NY, Abali H, Oksüzoğlu B et al. The efficacy and safety of reduced-dose docetaxel, cisplatin, and 5-fluorouracil in the first-line treatment of advanced stage gastric adenocarcinoma. Med Oncol 2010;27:680-684.
13. Chi Y, Ren JH, Yang L et al. Phase II clinical study on the modified DCF regimen for treatment of advanced gastric carcinoma. Chin Med J (Engl) 2011;124:2997-3002.
14. Greene FL, Page DL, Fleming ID (Eds): AJCC cancer staging manual (6th Edn): New York: Springer, 2002.
15. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer, 2013.
16. Dicken BJ, Graham K, Hamilton SM et al. Lymphovascular invasion is associated with poor survival in gastric cancer: an application of gene expression and tissue array techniques. Ann Surg 2006;243:64-73.
17. Deng J, You Q, Gao Y et al. Prognostic value of perineural invasion in gastric cancer: a systematic review and meta-analysis. PLoS One 2014;9:e88907.
18. Kim JJ, Kim JY, Hur H et al. Clinicopathologic significance of gastric adenocarcinoma with neuroendocrine features. J Gastric Cancer 2011;11:195-199.
19. Eren F, Celikel C, Güllüoğlu B. Neuroendocrine differentiation in gastric adenocarcinomas; correlation with tumor stage and expression of VEGF and p53. Pathol Oncol Res 2004;10:47-51.
20. Tamura T, Jobo T, Watanabe J et al. Neuroendocrine features in poorly differentiated endometrioid adenocarcinomas of the endometrium. Int J Gynecol Cancer 2006;16:821-826.
21. Allen FJ, Van Velden DJ, Heyns CF. Are neuroendocrine cells of practical value as an independent prognostic parameter in prostate cancer?. Br J Urol 1995;75:751-754.
22. Kim KH, Lee KW, Baek SK et al. Survival benefit of gastrectomy ± metastasectomy in patients with metastatic gastric cancer receiving chemotherapy. Gastric Cancer 2011;14:130-138.
23. Sarela AI, Yelluri S. Gastric adenocarcinoma with distant metastasis: is gastrectomy necessary?. Arch Surg 2007;142:143-149.
24. Wagner AD, Grothe W, Behl S et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2005;(2):CD004064.
25. Van Cutsem E, Moiseyenko VM, Tjulandin S et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-4997.
26. Kos FT, Uncu D, Ozdemir N et al. Comparison of cisplatin-5-fluorouracil- folinic acid versus modified docetaxel-cisplatin-5-fluorouracil regimens in the first-line treatment of metastatic gastric cancer. Chemotherapy 2011;57:230-235.
27. Inal A, Kaplan MA, Kucukoner M et al. Docetaxel and cisplatin plus fluorouracil compared with modified docetaxel, cisplatin, and 5-fluorouracil as first-line therapy for advanced gastric cancer: a retrospective analysis of single institution. Neoplasma 2012;59:233-236.