Int J Clin Exp Med 2017;10(3):5300-5306
www.ijcem.com /ISSN:1940-5901/IJCEM0028087

Original Article

Clinical characteristics and treatment options of patients with G3 gastroenteropancreatic neuroendocrine neoplasms in China

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Received March 13, 2016; Accepted May 26, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: Background: Well differentiated neuroendocrine tumor G3 (NET G3) patients are special parts of neuroendocrine neoplasms with a different biological behavior comparing with other G3 patients. The objective of our study was to investigate the clinical pathological features, the impact of different treatment strategies on their clinical outcomes of NET G3 and NEC in Chinese populations. Patients and Methods: We retrospectively collected 32 NET G3 patients from oncology departments of three hospitals in China and 38 neuroendocrine carcinoma (NEC) patients for comparison. Results: The most common primary site of NET G3 was pancreas (65.6%) followed by stomach and rectum. Esophageal and colon origin consisted almost one third of NEC but in none of NET G3. Significantly more NET G3 patients had hormone related symptoms and localized disease comparing with NEC. The median Ki-67 of NET G3 was 30% and median mitotic count was 12/10HPF which was lower than those of NEC and of the WHO criteria. In NET G3, overall response rate of temozolomide and capecitabine (TEMCAP) and platinum-based chemotherapy in the first-line or second-line settings was 11.8% (2/17) and 25.0% (3/12) (p=0.622), disease control rate was 81.3% (13/16) and 54.5% (6/11) (p=0.206), median progression-free survival (PFS) was 8.4 months (95% CI, 8.3-8.6) and 2.6 months (95% CI, 1.6-3.5) (p=0.061) respectively. The PFS of platinum-based therapy in NEC was 3.6 months. Conclusion: The clinical pathological features, histological characteristics and treatment response varied markedly between NET G3 and NEC. TEMCAP might be a promising treatment regimen for NET G3 patients that required further investigation.

Keyword: NET G3, neuroendocrine carcinoma, temozolomide, China

Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare types of tumors which express special diagnostic biomarkers. The heterogeneity of GEP-NENs determines different outcomes. According to 2010 World Health Organization (WHO) classification, GEP-NENs were divided into G1/G2/G3 based on the combination of mitotic count and Ki67 index. However, this grading system underestimated an important feature which was also a determine factor of NENs patients' outcome, the differentiation. Differentiation was regarded as the first prognostic factor and as the main determinant of the 2000 WHO classification.

Most of the G1/G2 neuroendocrine tumors (NETs) are well differentiated. G3 patients are supposed to be poorly differentiated defining as neuroendocrine carcinoma (NEC). However, approximate 10%-20% of G3 patients are well differentiated NETs (NET G3) with lower Ki-67 (mostly Ki-67<60%). The clinical characters and outcomes maybe different between NET G3 and other G3 patients. NET G3 patients are getting more attentions since they might be the key point for redefining the grading systems. This study was mainly focus on this special type of patients who were in the grey region in both 2000 and 2010 WHO classification. Our aim was to illustrate the clinical pathological features of NET G3 in Chinese population and to evaluate their clinical outcomes with different

Table 1. Basic characteristics in NET G3 and NEC patients

Characteristics	NET G3 (n=32), n (%)	NEC (n=38), n (%)	*P*-value
Age median (range)	53 (25-72)	58 (31-78)	
Gender			<0.001
Male	16 (50.0)	34 (89.5)	
Female	16 (50.0)	4 (10.5)	
Functional	5 (15.6)	0	0.017
Primary			<0.001
Pancreas	21 (65.6)	5 (13.2)	
Stomach	3 (9.4)	10 (26.3)	
Rectal	5 (15.6)	2 (5.3)	
Duodenal	1 (3.1)	1 (2.6)	
Unknown	1 (3.1)	4 (10.5)	
Esophageal	0	8 (21.1)	
Colon	0	4 (10.5)	
Other	1 (3.1)	4 (10.5)	
Staging			0.039
Local regional	9 (28.1)	3 (7.9)	
Distant	22 (68.8)	35 (92.1)	
Unknown	1 (3.1)	0	
Metastatic sites			
Liver	23/28 (82.1)	22/36 (61.1)	0.099
Lymph node	15/28 (53.6)	17/36 (47.2)	0.801
Bone	7/28 (25.0)	3/36 (8.3)	0.090
Peritoneum	5/28 (17.9)	2/36 (5.6)	0.225
Lung	3/28 (10.7)	1/36 (2.8)	0.311
Biomarkers			
CgA	13/20 (65.0)	6/11 (54.5)	0.705
NSE	15/25 (60.0)	18/30 (60.0)	1.000
SRS positive	17/22 (77.3)	10/17 (58.8)	0.299

CgA: Chromogranin A; NSE: Neuron-Specific Enolase; SRS: Somatostatin receptor scintigraphy.

treatment strategies in turn to help with future investigations.

Patients and methods

Medical oncology departments of three hospitals were involved in this study including Affiliated Hospital of Academy of Military Medical Sciences, China-Japan Friendship Hospital and Peking Union Medical College Hospital. All the GEP-NENs patients referred to these three hospitals from January 2009 to March 2015 were screened, and a total of 32 patients were pathologically diagnosed with NET G3. In 2013 Chinese pathologic consensus group for GEP-NENs proposed a new entity called "highly proliferative NET" which were defined as well differentiated NENs with Ki-67 level of 20-60% [1]. The pathologists who diagnosed these patients are fully experienced. Thirty-eight NEC patients from Affiliated Hospital of Academy of Military Medical Sciences during the same period were also enrolled. NEC was defined as poorly differentiated G3. Baseline characteristics and treatment response were collected for all those patients. Response rate was evaluated according to RECIST 1.1 criteria based on radiological imaging. The median follow-up time for all the 70 patients was 24.3 (21.0-27.6) months.

Statistical analysis

Statistical analysis was conducted by using SPSS 20.0 software. Comparison of various variables including baseline characters and response were analyzed by using the Pearson's χ^2 and Fisher's exact tests. Progression-free survival (PFS) was defined as the time from the first day of treatment to disease progression or to last follow-up, and was compared by using Kaplan-Meier method and log rank test. Statistical significance was determined at a p value of less than 0.05.

Results

Patient characteristics

Among NET G3 patients, the median age was 53, and 50% of them were male. The most common primary site was pancreas (65.6%), followed by rectal (15.6%) and stomach (9.4%). Liver (82.1%) and lymph node (53.6%) were the most common sites of metastasis. Baseline CgA and NSE were elevated in 65.0% and 60.0% of patients respectively. Somatostatin receptor scintigraphy was positive in 17 patients (77.3%). Nine patients had experienced radical surgery before developing metastatic disease with median disease free survival (DFS) of 12.0 months (95% CI 10.5-13.5).

Comparing with NET G3, NEC patients behaved differently. NEC was mainly composed of males (p<0.001), and the most common primary site was stomach, while pancreas was the second (p<0.001). The primary sites were esophagus

Table 2. Comparison of Ki-67 index and mitotic count in NET G3 and NEC patients

	NET G3		NEC	
Parameters	Ki-67 (%)	Mitotic count (/10HPF)	Ki-67 (%)	Mitotic count (/10HPF)
Total, median (range)	30 (20-60)	12 (1-30)	70 (25-90)	25 (1-150)
Primary sites, median (range)	25 (10-50)	10 (1-30)	75 (20-90)	25 (2-150)
Metastatic sites, median (range)	30 (20-60)	6 (1-26)	70 (25-80)	NA[a]

[a]Mitotic count of metastatic sites was reported in only 2 NEC patients, therefore the median mitotic count of metastatic sites was not available. NA: not available.

Table 3. Efficacy of different chemotherapies in NET G3 patients in first-line or second-line settings

Regimens	TEMCAP (n=17)	Platinum-based chemotherapy (n=12)	*P*-value
First line (n)	7	10	
Second line (n)	10	2	
Cycles, median (range)	6 (1-16)	3.5 (1-8)	
RR			
PR, n (%)	2 (11.8)	3 (25.0)	0.622
SD, n (%)	11 (64.7)	3 (25.0)	0.041
PD, n (%)	3 (17.6)	5 (41.7)	0.158
NA, n (%)	1 (5.9)	1 (8.3)	1.000
DCR, n (%)	13 (81.3)	6 (54.5)	0.206
Median PFS (95% CI), months	8.4 (8.3-8.6)	2.6 (1.6-3.5)	0.061

RR: response rate; PR: partial response; SD: stable disease; PD: progression disease; NA: not available; DCR: disease control rate; PFS: progression-free survival; TEMCAP: temozolomide and capecitabine.

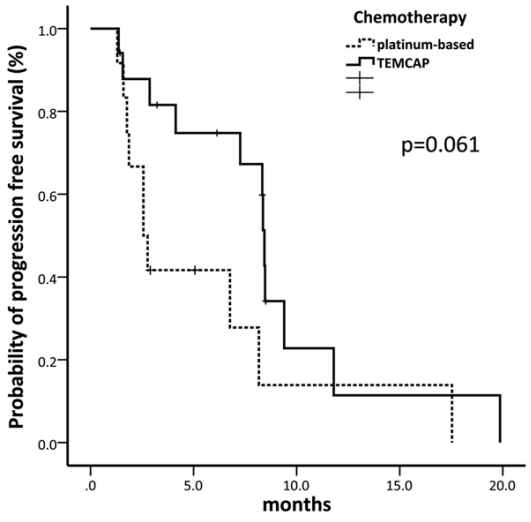

Figure 1. Comparison of PFS in NET G3 patients receiving TEMCAP and platinum-based chemotherapy in first-line or second-line settings. TEMCAP: temozolomide and capecitabine.

(21.1%) and colon (10.5%) in almost one third of NEC patients but in none of NET G3 patients. Five (15.6%) patients in NET G3 group and none in NEC group had hormone related symptoms at diagnosis. Significantly fewer NEC patients had localized disease (p=0.039). A trend of higher proportion of liver and bone metastases was observed in NET G3 as compared with NEC. Patient characteristics of NET G3 and NEC were listed in **Table 1**.

Pathological characterization

Ki-67 index were all below 60% with a median of 30% in NET G3 patients. On the contrary, NEC had a much higher median Ki67 index than the lower limit of the WHO classification for G3 (**Table 2**). Median mitotic count of NET G3 was 12/10HPF, which was also lower than that of NEC and of the WHO classification.

Treatments

Palliative treatment was given to 27 NET G3 patients and 32 NEC patients. In NET G3 group, a total of 17 patients had received temozolomide and capecitabine (TEMCAP) therapy and 12 patients had received platinum-based therapy in first-line or second-line settings. The overall response rate (RR) of TEMCAP and platinum-based chemotherapy was 11.8% (2/17) and 25.0% (3/12) (p=0.622), and disease control rate (DCR) was 81.3% (13/16) and 54.5% (6/11) (p=0.206), respectively (**Table 3**). Median PFS was 8.4 months (95% CI, 8.3-8.6) in the TEMCAP group, as compared with 2.6 months (95% CI, 1.6-3.5) in the platinum-based chemotherapy group (p=0.061) (**Figure 1**).

Table 4. Efficacy of platinum-based chemotherapy in NET G3 and NEC patients in first-line settings

	NET G3 (n=10)	NEC (n=28)	*P*-value
Cycles, median (range)	3 (1-6)	2.5 (1-8)	
RR			
PR, n (%)	3 (30.0)	7 (25.0)	1.000
SD, n (%)	2 (20.0)	10 (35.7)	0.453
PD, n (%)	4 (40.0)	8 (28.6)	0.694
NA, n (%)	1 (10.0)	3 (10.7)	1.000
DCR, n (%)	5 (55.6)	17 (68.0)	0.357
Median PFS (95% CI), months	2.6 (1.6-3.5)	3.6 (0.9-6.4)	0.318

RR: response rate; PR: partial response; SD: stable disease; PD: progression disease; NA: not available; DCR:disease control rate; PFS: progression-free survival.

Two patients experiencing partial response to TEMCAP in NET G3 were both pancreatic origin. The DCR of TEMCAP in 11 pancreatic and 5 gastrointestinal NET G3 patients were 72.7% and 80.0% respectively.

In NET G3 and NEC patients who had received platinum-based chemotherapy in first-line settings, RR was 30.0% (3/10) and 25.0% (7/28) respectively. There was no significant differences between PFS of the two groups (2.6 months vs 3.6 months, p=0.318) (**Table 4**).

Since less than half NET G3 patients have died at the time of analysis, the overall survival was not assessed.

Discussion

In the past few decades, the WHO classification standard had been modified several times. In 2000, the classification was based on differentiation and metastases, and in 2010 it was mainly based on Ki-67 and mitotic count [2]. Previous studies had shown that patients with well differentiated, high-grade NET had worse outcome than patients with intermediate-grade tumors but had better outcome than those of patients with poorly differentiated NEC.

In our study, the most common primary site of NET G3 patients was pancreas, followed by rectum and stomach, which was quite accordance with a recent study of 37 NET G3 reported by Heetfeld et al. [3]. However, in Heetfeld et al.'s study, 5% of the patients' primary sites were small intestine, while none was observed in our study. In western nations, 30-60% of GEP-NENs were derived from midgut [4, 5]. Previous Chinese study had reported a much lower percentage of small intestinal NETs which was also indicated in the studies of Japan, Korea and Taiwan, about 1.9-7.7% [6-10]. Moreover, the percentage of esophageal NEC (21.1%) was higher in this study compared with other NEC studies (4-5%) [3, 11] suggesting that the distribution of primary tumors in GEP-NENs might be different between Caucasian and Asian. Approximately 24-30% [3, 11] of NEC were colon or esophageal origin but none of NET G3 was reported until now. NORDIC study indicated that colon G3 patients had a significantly lower OS than pancreatic G3 patients (8 vs 15 month). One hypothesis is that the poorly differentiated tumor in colon and the well differentiated tumor in pancreas might contribute to the significant survival difference. Therefore, our results suggested that esophageal and colon G3 patients were generally poorly differentiated.

Diagnosing NET G3 required two indicators: Ki-67 index and differentiation. The Ki-67 of NET G3 was reported generally less than 50%, with a median level of 25-30% [12], which was consistent with our study. Our data also presented that the level of Ki-67 and mitotic count in NET G3 was much lower than NEC, and the median mitotic count was below the WHO criteria of G3. Basturk et al. [13] had reported the mitotic count of 19 well differentiated pancreatic NET G3 were all lower than 20/10HPF. Since differentiation did not have a clear definition and difficult to distinguish in daily practice, in this case mitotic count might be an useful assistant diagnostic index for NET G3.

Only 2 articles until now had referred to the palliative treatment of EP regimen for NET G3 patients as the only approved therapy [3, 14]. Results from our analysis showed that in 10 NET G3 patients treated with platinum-based therapy in first-line settings, RR was 30.0% and PFS was 2.6 months, which was reasonably in line with Heetfeld et al.'s study which presented 12 cases with RR of 17% and PFS of 2.4 months. However inconsistent with the prior study [3], neither DCR nor PFS showed signifi-

cant differences between NET G3 and NEC patients in our study. PFS of EP regimen treating poorly differentiated NEC in the previous studies was about 4.0-11.0 months [3, 15, 16]. In contrast, PFS of our study (3.6 months) was relatively short which may be associated with small sample sizes of NEC Group. Although without significant differences, when combining the data of other NEC studies, we found the PFS of 2.6 months was quite short for the NET G3 patients which indicated that the role of platinum-based chemotherapy in NET G3 patients was questionable comparing with NEC.

Previous studies of small samples had reported the treatment of TEMCAP regimen for NET G2 patients, RR varied widely from 15% to 70%. DCR and PFS was 80% to 97% and 11.0 month to 18 month, respectively [17-20]. Disease control rate was 81.3% in NET G3 patients in our study, which was close to the previous report of NET G2. But the PFS of NET G3 was evidently shorter than well differentiated NET G2. Considering efficacy, both partial response patients were pancreatic origin which was quite accordant with the previous reports on the effect of this regimen [17, 18]. In the 4 out of 5 patients with gastrointestinal origin (stomach, duodenum and rectum), the tumors were stabilized for more than six months. Although the efficacy of TEMCAP for gastrointestinal NET G3 patients might be inferior to pancreatic origin, this regimen also might be an optional choice.

This study indicated that TEMCAP regimen was marked superior to platinum-based therapy on PFS (p=0.061). NORDIC study suggested that the response rate of EP/EC in patients with Ki-67>55% was significantly higher than those with Ki-67<55%. Referring to lower Ki-67 index patients, this study suggested better efficacy of TEMCAP for well differentiated NET G3 than platinum-based therapy. However, for poorly differentiated NEC with a lower Ki-67 index, which regimen is better? Welin et al. [21] found that poorly differentiated patients who didn't respond to first-line chemotherapy seemed to respond more often to second-line therapy than patients who had responded to first-line chemotherapy. Moreover, they found more responder of TEMCAP with Ki-67<60%. But there had been no studies comparing the efficacy of platinum-based therapy and TEMCAP in NEC patients with Ki-67<60%. Since our study had only 7 NEC cases with Ki-67<60%, and none of them had been treated with TEMCAP, we're unable to answer this question.

The significant differences between well differentiated NET G3 and poorly differentiated NEC was a challenge for 2010 WHO classification, however whether it should be reclassified according to Ki-67 or differentiation was still unclear. Although several studies had illustrated that NET G3 had better prognosis than NEC, none of them had compared the differentiation differences in the populations of Ki-67<60%. In Welin's study, 16 out of 25 patients with poorly differentiated non-small cell NEC had Ki-67 less than 60%, positive rate of Somatostatin receptor scintigraphy was 70%, and median overall survival was 22 months [21]. These data shed light on the possible one or a cohort of prognostic factors for G3 tumors with relatively lower Ki-67 index.

Conclusion

To our knowledge, this is the first data of NET G3 in Asian populations. Clinical pathological features, histological characteristics and treatment response varied markedly between NET G3 and NEC. The most common primary site of NET G3 was pancreas. TEMCAP might to be a promising treatment regimen for NET G3 patients which demands further investigation.

Acknowledgments

The authors thank Professor Jie Luo (China-Japan Friendship Hospital), Xiao-Yan Chang (Peking Union Medical College Hospital) and Yan-Hong Tai (Affiliated Hospital Cancer Center, Academy of Military Medical Sciences) for reviewing the pathological slides of all these patients.

Disclosure of conflict of interest

None.

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