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Original Article

Toxicities, safeties and clinical response of dacarbazine-based chemotherapy on neuroendocrine tumors in Taiwan population

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Abstract

Background: Currently, the role of dacarbazine (DTIC) based chemotherapy in neuroendocrine tumors (NETs) in Asia is unclear. Here, we report the outcomes of dacarbazine (DTIC)-based chemotherapy in Taiwan population.
Methods: DTIC alone (250 mg/m^2/day), or 5-fluorouracil (5-FU, 500 mg/m^2/day) and DTIC (200 mg/m^2/day) with or without epirubicin (200 mg/m^2/day), for 3 days, every 3−4 weeks. Subgroups were analyzed by grading, and by Ki-67 index.
Results: 48 patients were reviewed in this study, including 3 had grade 1 tumors, 23 had grade 2, while 22 were grade 3. In grade 3 NEC patients, the tumor Ki-67 index of 21−55% were noted in 8 patients, and >55% in 14 patients. Progression-free survival (PFS) was 5.1 months, and overall survival (OS) was 31.6 months. The PFS (in months) were 12.5 and 1.8 for patients with NETs and neuroendocrine carcinomas (NECs), respectively ($p < 0.001$). The OS were not reached and 5.9 months for patients with NETs and NECs, respectively ($p = 0.001$). Patients with NECs were divided into two groups, according to their Ki-67 index. In patients with a tumor Ki-67 index of 21−55%, PFS was 4.1 months, and OS was not reached; in those with a tumor Ki-67 index of >55%, they were 1.5 and 1.8 months, respectively ($p < 0.001$ and $p = 0.013$).
Conclusion: NETs, and grade 3 NECs, with Ki-67 indices of 20−55% had good responses to DTIC-based chemotherapy, with acceptable side effects. Ki-67 index could predict prognosis for grade 3 NEC patients, and guide further chemotherapy choices.

Keywords: Dacarbazine; Ki-67 index; Neuroendocrine carcinoma; Neuroendocrine tumors; Overall survival; Progression-free survival

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Neuroendocrine tumors (NETs) are rare neoplasms characterized by heterogeneous behavior, and have the ability to secrete a variety of hormones, resulting in various clinical syndromes.[1] Although NETs are rare diseases, their incidence has steadily increased over five times in the past 30 years.[2] The prognosis of NETs is heterogeneous. Therefore, World Health Organization (WHO) classified gastroenteropancreatic neuroendocrine tumors (GEP-NETs) into NET grade 1 (G1), NET grade 2 (G2), and neuroendocrine carcinoma (NEC) grade 3 (G3) based on their Ki-67 proliferation index.[3] Surgical resection is the only potentially curative therapy.[4] However, most patients are diagnosed with advanced stage disease.[2,3] Therapeutic options for metastatic G1 and G2 GEP-NET treatment include hormone therapy with a somatostatin analog; targeted therapy; interferon-α therapy; and transcatheter arterial chemoembolization and radiofrequency ablation for local regional control.[4,5] Chemotherapy may be more appropriate as early-line therapy in patients with bulky, or symptomatic, or rapidly progressive tumors, particularly of pancreatic origin.[6] Standard frontline treatment for metastatic G3 NEC uses a combination of etoposide and cisplatin (EP), for which the median duration of response is about 8−9 months.[7−9] An alternative chemotherapy regimen—a combination of streptozotocin, 5-fluorouracil (5-FU), and doxorubicin—was proposed for treating G1 and G2 NETs. However, due to the renal toxicity of streptozotocin, temozolomide, or dacarbazine (DTIC), was substituted in some countries, and the response rates were 16−30% in the previous study.[7,10−12]

Grade 3 NECs are a heterogeneous group, and not considered a single disease entity. Sorbye et al. demonstrated that NECs could be further classified using a Ki-67 index cutoff of 55%.[13] Patients with a tumor Ki-67 index of <55% had a lower response rate to cisplatin-based chemotherapy, but they survived longer compared to patients with a tumor Ki-67 index of ≥55%.[13] NEC patients with tumor Ki-67 indices of 21−55% had better prognoses, irrespective of platinum-based chemotherapy treatment. This finding may lead to the selection of another chemotherapy regimen, rather than EP, for patients with a tumor Ki-67 index of <55%. Some case studies have suggested that DTIC-based chemotherapy could be the second-line treatment, after frontline treatment with etoposide and cisplatin.[13,14] However, no study has investigated use of this regimen in Asia, as either frontline or second-line treatment. In this study, we retrospectively evaluated tumor response, progression-free survival, and overall survival for NET patients who received DTIC-based chemotherapy.

2. Methods

2.1. Study population

This study has been approved by the Ethics Committee of Taipei Veterans General Hospital and Chang Gung Memorial Hospital. Clinical data, including, age; gender; Tumor-Node-Metastasis staging information; tumor site; performance status; functioning symptoms; and, side effects of chemotherapy were obtained through a detailed retrospective review of the medical records of 48 patients with NETs, who had received DTIC-based chemotherapy between January 2010 and January 2016.

In all cases, histological diagnosis was confirmed by two pathologists, and classification of NETs was based on the WHO classification.[3]

Grade of histological differentiation, immunohistochemistry, and Ki-67 staining index were assessed.

2.2. Treatment and evaluation

2.2.1. Regimen

The chemotherapy regimen consisted of the intravenous administration of dacarbazine (220 mg/m^2/day) alone for 3 days, every 3 weeks; 5-FU (500 mg/m^2/day) and dacarbazine (200 mg/m^2/day) with (FDE) or without (FD) epirubicin (200 mg/m^2/day) for 3 days, every 3−4 weeks. If feasible, and in the absence of disease progression after 3 cycles, at least 6 cycles were scheduled. Antiemetics were administered at each course of therapy. Granulocyte colony-stimulating factor was used as secondary prophylaxis in most patients, and as primary prophylaxis in frail patients.

2.2.2. Response, survival, and toxicity evaluation

Computed tomography scan was used for tumor restaging every 3 months, or performed to document disease progression based on clinical symptom deteriorated, and response was assessed using RECIST 1.1. After discontinuation of treatment, patients with no clinical progression symptoms were followed up every 3 months, until disease progression or death. Disease control rate was defined as complete response, partial response, or stable disease. Overall survival (OS) was defined as the time from receiving DTIC based chemotherapy until the date of death due to any cause, or, until the date when lost to follow-up. Progression-free survival (PFS) was defined as the time from receiving DTIC based chemotherapy until the date of documented disease progression, relapse, or death due to any cause; or the date when lost to follow-up after DTIC-based therapy. Toxicity was evaluated and recorded, according to version 4.0 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute.

2.3. Statistics

Categorical variables were expressed as percentages, and continuous variables were presented as median (range, minimum to maximum). The χ^2 test or Fisher's exact test was used to assess qualitative variables. Results were considered significant if p values were <0.05. The distributions of PFS and OS were estimated by Kaplan−Meier curve and log-rank test analyses. Kaplan−Meier curve analyses were performed for PFS and OS, using SigmaPlot version 12.5 (Systat Software, Inc.).

3. Results

3.1. Patient characteristics

There were 35 male and 13 female patients enrolled in our study. Their clinical features are shown in Table 1. The most common primary tumor sites were the pancreas (n = 30, 62.5%), the gastrointestinal tract (n = 6, 12.5%), others (n = 3, 6.3%, 2 thymus tumors and 1 ethmoid sinus tumor), and those of unknown origin (n = 9, 18.7%). All primary sites from the gastrointestinal tract were grade 3 tumors. Three (6.3%) patients had grade 1 tumors, 23 patients (47.9%) had grade 2 tumors, and 22 patients (45.8%) had grade 3 tumors. In grade 3 NEC patients, the tumor Ki-67 index was 21–55% in 8 patients, and >55% in 14 patients. Forty patients (83.3%) were diagnosed with stage IV disease. The majority of patients had liver metastasis (38 patients, 79.2%). Four patients (8.3%) had lung metastasis; 10 (20.8%), bone metastasis; and, 9 (18.8%), metastasis to other sites (peritoneal seeding, spleen invasion, and orbital metastasis).

Table 1
Patient characteristics.

Patient characteristics		Number	%
Sex	Male	35	73%
	Female	13	27%
Median age, years (Range)		58.5	(22–89)
Tumor origin	Pancreas	30	62.5%
	GI tract	6	12.5%
	Others	3	6.3%
	Unknown	9	18.7%
WHO grade	Grade 1	3	6.3%
	Grade 2	23	47.9%
	Grade 3	22	45.8%
Ki-67%	<2%	3	6.3%
	2–20%	23	47.9%
	21%–55%	8	16.7%
	>55%	14	29.1%
TNM stage	Stages 0–III	8	16.7%
	Stage IV	40	83.3%
Metastasis	Liver	38	79.2%
	Lung	4	8.3%
	Bone	10	20.8%
	Others	9	18.8%
Disease status during DTIC-based therapy	Progressed disease	36	75%
	Newly diagnosed	12	25%
Performance status (ECOG)	0	7	14.6%
	1	29	60.4%
	2	8	16.7%
	3	4	8.3%
	4	0	0%
Prior treatment	Resection of primary tumor	15	31.3%
	Octreotide	14	29.2%
	EP	36	75%
	TAE/TACE/RFA	5	10.4%
Functioning symptoms	Diarrhea	3	6.3%
	Flushing	1	2.1%
	Gastric ulcer	3	6.3%
	No functioning symptoms	41	85.3%
Regimen	DTIC alone	14	29.2%
	FD	12	25%
	FDE	22	45.8%
Cycles of DTIC-based chemotherapy	1	8	16.7%
	2	7	14.6%
	3	8	16.7%
	4	9	18.7%
	5	1	2.1%
	6	9	18.7%
	>6	6	12.5%

Abbreviations: GI tract = gastrointestinal tract; WHO = World Health Organization; TNM = tumor-node-metastasis; DTIC = dacarbazine; PVP = Cisplatin-etoposide; TAE = transcatheter arterial embolization; TACE = transcatheter arterial chemoembolization; RFA = radiofrequency ablation; FD = 5-FU + dacarbazine; FDE = 5-FU + dacarbazine + epirubicin.

3.2. Prior treatment and DTIC-based chemotherapy

Thirty-six patients (75%) experienced frontline-treatment failure, and the remaining 12 (of 48) patients were newly diagnosed. Fifteen patients had previously received surgery, and 14 patients had received prior hormone therapy with somatostatin analogs. Thirty-six patients received chemotherapy with EP, and 5, received other interventions, such as transcatheter arterial embolization, transcatheter arterial chemoembolization, or radiofrequency ablation. Fourteen patients received chemotherapy with DTIC alone; 11, with FD; 22, and with FDE; 2. Detailed information on prior treatments and DTIC-based chemotherapy is listed in Table 1.

3.3. Treatment response and survival in patients receiving DTIC-based chemotherapy according to WHO 2010 classification

Excluding the one patient who was unevaluable, 4 patients had complete responses; 11, partial responses; 12, stable disease; and 20, progressive disease after DTIC-based regimens (Table 2). The objective response rate was 31.3%, and the disease control rate was 56.2%. The median follow-up time was 10.5 months. The PFS for all patients was 5.1 months (95% confidence interval [CI]; range, 2.75–7.43), and the OS was 31.6 months (95% CI; range, 0–64.44). The PFS for patients with grade 1 and 2 NETs was significantly better than that of those with grade 3 NECs (Fig. 1). The PFS was 12.5 months (95% CI; range, 5.4–20.0) in patients with grade 1 and grade 2 NETs, while patients with grade 3 NECs had a PFS of only 1.8 months (95% CI; range, 0.70–3.22; $p < 0.001$, Fig. 1). The OS times were not reached, and 5.95

Table 2
Response to dacarbazine-based chemotherapy.

WHO Grade	Ki-67 (%)	CR	PR	SD	PD	Unevaluable	Total
1	<2	0 (0)	0 (0)	3 (100)	0 (0)	0 (0)	3
2	2–20	4 (17)	7 (31)	7 (31)	4 (17)	1 (4)	23
3	>20	0 (0)	4 (18)	2 (9)	16 (73)	0 (0)	22

Abbreviations: WHO = World Health Organization; CR = Complete Response, PR = Partial Response; SD = Stable Disease; PD = Progressive Disease.

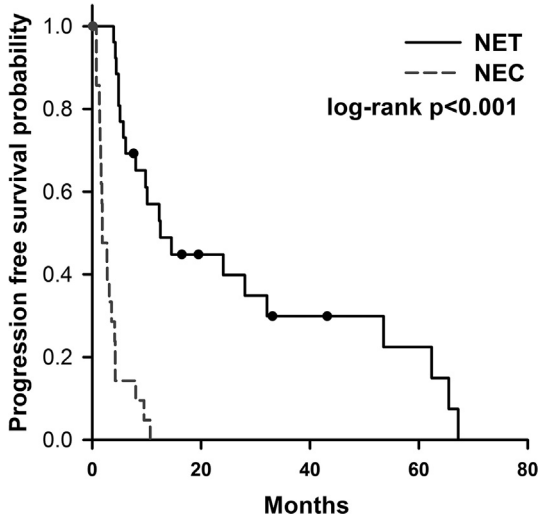

Fig. 1. Kaplan–Meier curves for the progression-free survival of 48 patients diagnosed with NETs, according to their WHO grading.

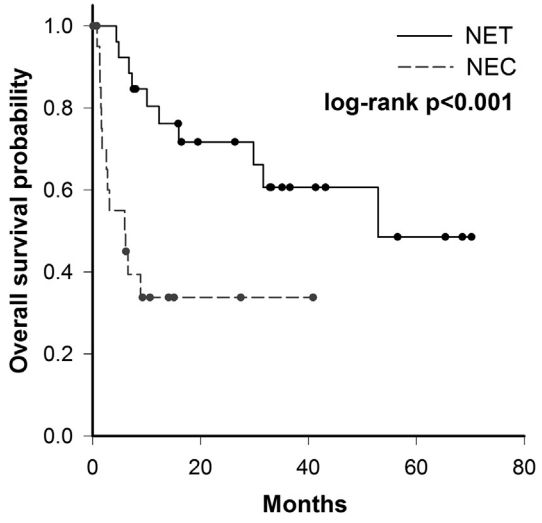

Fig. 2. Kaplan–Meier curves for the overall survival of 48 patients diagnosed with NETs, according to their WHO grading.

months (95% CI; range, 0–12.50) for patients with grade 1 and grade 2 NETs, and grade 3 NECs, respectively ($p < 0.001$, Fig. 2). Regarding the 12 fresh cases treated with DTIC based therapy, the response rate was 33% and the detail information was illustrated in supplemental table.

3.4. Treatment response and survival in grade 3 NEC patients according to Ki-67 index

Patients with grade 3 NECs were subdivided into two groups, according to their Ki-67 staining percentage index. Although not statistically significant, patients with a tumor Ki-67 index of 21–55% trended towards better disease control rates than those with a tumor Ki-67 index of >55% (50% vs. 14%; $p = 0.096$, Table 3). The PFS was 4.1 months (95% CI; range, 0.47–5.03) in patients with a tumor Ki-67 index of 21–55%, and 1.5 months (95% CI, range, 0.17–1.88) in those

Table 3
Response to dacarbazine-based chemotherapy in grade 3 NEC patients.

Response	Ki-67		
	21–55% (n = 8)	>55% (n = 14)	*p*
PR	3 (38)	1 (7)	
SD	1 (12)	1 (7)	0.096
DCR (PR + SD)	4 (50)	2 (14)	
PD	4 (50)	12 (86)	

Abbreviations: WHO = World Health Organization; PR = partial response; SD = stable disease; DCR = disease control rate; PD = progressive disease. *p* value is calculated by Fisher's exact test for DCR in Ki-67 index of 21–55% vs. >55%.

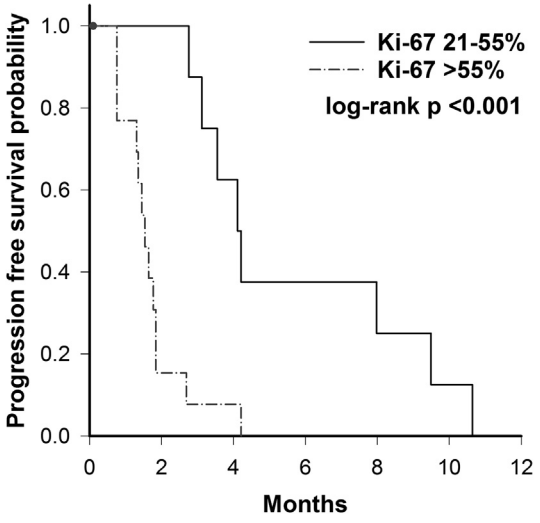

Fig. 3. Kaplan–Meier curves for the progression-free survival of 22 patients with diagnosed with NECs, according to their Ki-67 staining.

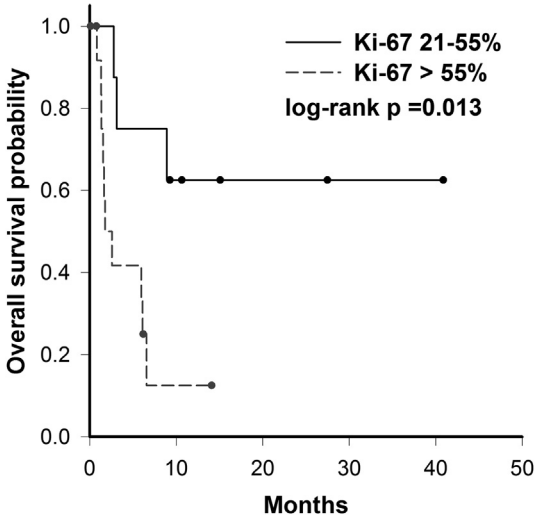

Fig. 4. Kaplan–Meier curves for the overall survival of 22 patients diagnosed with NECs, according to their Ki-67 staining.

with a tumor Ki-67 index of >55% ($p < 0.001$; Fig. 3). The OS was not reached in patients with a tumor Ki-67 index of 21–55%, and 1.8 months (95% CI; range, 0.21–3.33) in those with a tumor Ki-67 index of >55% ($p = 0.013$; Fig. 4).

Table 4
Side effects of dacarbazine-based chemotherapy.

Side effects	Number of patients	%
Anemia, grade 1–2	5	10.4%
Anemia, grade 3–4	6	12.5%
Neutropenia, grade 3–4	7	14.6%
Febrile neutropenia	2	4.2%
Thrombocytopenia, grade 3–4	3	6.3%
Nausea/vomiting, grade 1–2	10	20.8%
Nausea/vomiting, grade 3–4	0	0%
Diarrhea, grade 1–2	1	2.1%
Diarrhea, grade 3–4	1	2.1%

3.5. Adverse effects

Grade 3–4 hematological toxicities are listed in Table 4. Seven (14.6%) patients experienced grade 3–4 neutropenia; 6 (12.5%), anemia; 3, thrombocytopenia; and 2, febrile neutropenia. Ten patients had grade 1–2 nausea/vomiting; and 1, grade 1–2 diarrhea.

4. Discussion

The combination of 5-FU, dacarbazine, and epirubicin for treatment of NETs was first advocated by Bajetta et al., who reported an overall response rate of 24–30% in chemotherapy-naive patients.[8,15,16] Our study, which is the first one investigating DTIC-based chemotherapy for Asian patients with NETs, reports an objective response rate of 31.3%, and a disease control rate of 56.2%. On the other hand, Walter et al. reported a disease control rate of 83% in 29 patients receiving salvage therapy.[17] This discrepancy may be the result of including patients with different characteristics. In contrast to the Walter et al. study, in which most patients had grade 1 or 2 NETs, more than half of our patients had grade 3 NECs. The disease control rate was 92.8% in grade 2 NET patients, which was similar to that found by Walter et al.[17] This suggests that DTIC-based chemotherapy is also effective for Asian NET patients.

Our study reported a PFS of 5.1 months, and an OS of 31.6 months in the entire patient population, while patients with grade 1 and grade 2 NETs had a PFS and OS of 12.5 and not reached, respectively; which was compatible with the values obtained in other studies.[10,15,17] The prospective study, Eastern Cooperative Oncology Group Study E1281,[18] demonstrated that patients with carcinoid tumors that were treated with streptozotocin and fluorouracil had a PFS of 5.3 months, and an OS of 24.3 months, which is similar to our findings. A previous study revealed that the time to progression, and median OS were only 2.3 months and 17.6 months, respectively, for patients with well-differentiated NETs treated with platinum-based therapy (EP).[8] Although the comparison is not exact, DTIC-based chemotherapy seems more efficacious than EP chemotherapy, for those with well-differentiated NETs, per the review of literature,[10,15,17] and, the findings of our study.

However, the prognosis for patients with grade 3 NECs remained poor, and most patients died within one year of diagnosis. Although all grade 3 NEC patients have dismal prognoses, in general, NEC is a heterogeneous disease. In 2012, Sorbye et al. used a tumor Ki-67 staining index of 55% as a cutoff to predict the prognosis of grade 3 NEC patients, and used this to determine if further chemotherapy should be introduced.[13] Patients with a tumor Ki-67 index of <55% had an OS of 14 months, which was significantly better than the OS for those with a tumor Ki-67 index of ≥55%. However, when treated with platinum-based chemotherapy, patients with a tumor Ki-67 index of <55% had lower response rates than those with a tumor Ki-67 index of ≥55% (15% and 42%, respectively; $p < 0.001$). Platinum-based chemotherapy did not affect response rate or survival.[13] This important finding suggests that grade 3 NECs do not necessarily comprise a single disease entity. This finding may necessitate the choice of another chemotherapy, such as a DTIC-based regimen instead of EP, for those patients with a tumor Ki-67 index of <55%. According to the Eastern Cooperative Oncology Group-E6282 study,[9] the response rate was 34% for advanced pancreatic islet neuroendocrine carcinoma patients treated with DTIC. In addition, Bajetta et al. also had demonstrated the clinical benefit in 53% of neuroendocrine carcinoma patients treated with FDE.[15] These results were compatible with our finding in Taiwan population. In our study, we treated these grade 3 NEC patients with DTIC-based chemotherapy, and found that patients with tumor Ki-67 indices of 21–55% had better disease control rates than those with tumor Ki-67 indices of >55%. Furthermore, significantly better PFS was noted for patients with a tumor Ki-67 index of 21–55%, who were treated with DTIC-based chemotherapy. Our data confirmed that using a tumor Ki-67 index of 55% could predict prognosis for grade 3 NEC patients, and DTIC-based chemotherapy could be an alternative regimen for NEC patients, especially those with a tumor Ki-67 index of <55%. Another second-line regimen that has been investigated is temozolomide-based chemotherapy. Welin et al. demonstrated a PFS of 6 months, and an OS of 22 months for patients with poorly differentiated NECs, who progressed after first-line treatment with temozolomide alone, or combined with capecitabine.[19] Both temozolomide and DTIC are prodrugs of the active alkylating agent 5-(3-methyltriazen-1-yl)imidazole- 4-carboximide and have equal efficacy.[20] In this study, more patients with a tumor Ki-67 index of <60% responded to therapy than those with a tumor Ki-67 index of ≥60%.[19] Therefore, current ENETS consensus guidelines also suggest to consider to use temozolomide based chemotherapy in well differentiated NET G3 (Ki67 index of 20–55%).[21]

Treatment-related toxicity was an important concern in the management of patients with NETs. When using EP therapy, grade 3–4 hematological toxicities were noted in 60% of patients,[8] and 40% developed grade 3–4 gastrointestinal toxicities. Maire et al. reported that 5 of 21 (24%) patients with NETs who were treated with oral temozolomide developed grade 3 or 4 toxicity,[12] while Welin et al. demonstrated that only 1 of 25 patients experienced grade 3 thrombocytopenia and leucopenia.[19] When treating patients with DTIC-based chemotherapy, Walter et al. reported that grade 3–4 neutropenia developed in 14 of 39 (35.8%) patients, and grade 3–4 anemia developed in 3 of 39 (7.6%) patients.[17] In our study, 7 of 48 (14.6%) of our patients developed grade 3–4

neutropenia, and 6 (12.5%) patients experienced grade 3−4 anemia; 2 of these also experienced upper gastrointestinal bleeding at the same time. Compared with previous studies, there were slightly fewer adverse events in our study.[8,12,15−17,19] Therefore, we inferred that DTIC-based chemotherapy is relatively safe and efficacious for Asian patients with NETs. Further studies should be conducted to evaluate use of DTIC-based chemotherapy as frontline treatment for patients with a NEC Ki-67 index of 21−50%.

This was a retrospective study. Therefore, it included some inherent limitations. Because NETs are rare, the patient number in our study was too small to draw any firm conclusions about predictive factors for response to DTIC-based chemotherapy in NET patients. However, this study enrolled most cases in two largest medical center and it's a first report for Asian population. Although the patient number was limited, we still noted that a tumor Ki-67 index of 55% was an important predictor of response and survival in Asian patients with NETs. In addition, we were not able to control for or select patients with underlying comorbidities or previous treatments that may interfere with treatment response and survival. However, among those 22 patients with Ki-67 >20%, only one patient was newly diagnosed and the response or survival remained unchanged even excluding this case (Data not shown). It indicated that DTIC-based therapy was an optimal second line therapy for patient with Ki67 of 20−55%. In the future, prospective studies of 1st line or second line DTIC-based chemotherapy in G3 NEC (Ki-67 of 10−55%) should be performed.

In conclusion, NET patients with a tumor Ki-67 index of less than 55% had good responses to DTIC-based chemotherapy, with acceptable side effects. The Ki-67 percentage index could predict prognosis for grade 3 NEC patients, and could be used to determine further chemotherapy.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jcma.2017.08.020.

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