Original Article

Etoposide and Cisplatin Versus Irinotecan and Cisplatin as the First-Line Therapy for Patients With Advanced, Poorly Differentiated Gastroenteropancreatic Neuroendocrine Carcinoma: A Randomized Phase 2 Study

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BACKGROUND: Platinum-based chemotherapy is recommended for the treatment of advanced gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC). The objective of the current phase 2 study was to compare the efficacy and toxicity between etoposide and cisplatin (EP) and irinotecan and cisplatin (IP) as first-line treatment in patients with advanced GEP-NEC. **METHODS:** Patients with advanced, poorly differentiated GEP-NEC randomly were assigned to receive EP or IP. The primary endpoint was the objective response rate (ORR). The secondary endpoints were progression-free survival, overall survival, and toxicities. **RESULTS:** The planned size of the study population was 144 patients, but enrollment was terminated early at 66 patients because the premature analysis found similar responses in the 2 treatment arms. The ORRs of the EP and IP arms both were 42.4% (14 of 33 patients). The efficacy was similar for small cell NEC with EP or IP (63.2% and 61.5%, respectively; $P = .61$), whereas that of IP was slightly better in patients with non–small cell NEC (30% vs 14.3%; $P = .42$). The median progression-free survival was 6.4 months and 5.8 months, respectively, for the EP and IP arms ($P = .81$), and the median overall survival was 11.3 months and 10.2 months, respectively, for the EP and IP arms ($P = .37$). The incidence of grade 3/4 neutropenia was significantly higher in the EP arm compared with the IP arm (45.4% vs 12.1%; $P = .002$). Nonhematological toxicity was relatively mild and more frequent in the IP arm compared with the EP arm (54.5% vs 18.2%; $P = .001$). No toxicity-related deaths were reported. **CONCLUSIONS:** The results of the current study demonstrated that IP is not inferior to EP, with comparable efficacy for poorly differentiated NEC of the digestive system. In addition, both regimens appear to be well tolerated with diverse toxicity profiles. ***Cancer* 2020;126:2086-2092**.

KEYWORDS: chemotherapy, etoposide and cisplatin (EP), gastroenteropancreatic, irinotecan and cisplatin (IP), neuroendocrine carcinoma.

INTRODUCTION

Gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) is a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system. In the 2017 World Health Organization (WHO) classification,[1] neuroendocrine neoplasms are classified histologically based on differentiation (well or poorly differentiated), Ki-67 index, and mitotic count. Poorly differentiated NEC has a Ki-67 index of 20% and/or a mitotic count of >20 per 10 high-power fields. In the Surveillance, Epidemiology, and End Results database, GEP-NEC has a poor spontaneous prognosis, with a median survival of 4 to 6 months in the absence of treatment.[2] Although palliative chemotherapy is the standard therapeutic modality for patients with advanced GEP-NEC, to the best of our knowledge the optimal regimen has yet to be identified.

Treatment guidelines recommend the use of cisplatin combined with etoposide (EP regimen) for patients with advanced extrapulmonary NEC because NEC resembles small cell lung cancer (SCLC).[3,4] In 2002, a randomized phase 3 trial (Japanese Clinical Oncology Group 9511) demonstrated better response and survival in patients with extensive-stage SCLC who were treated with irinotecan and cisplatin (IP regimen) compared with those treated with EP.[5] A recent Korean study also demonstrated no significant differences in overall survival (OS) and progression-free survival (PFS) between the IP and EP treatment arms for SCLC.[6] Furthermore, a large Japanese, retrospective, multicenter study of patients with advanced NEC of the digestive system reported a higher response rate

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(RR) and survival among those treated with IP (160 patients) compared with EP (46 patients) (RR: 50% vs 28%; OS: 13.0 months vs 7.3 months).[7] However, to our knowledge, no randomized controlled trial has been conducted to date, and retrospective reports have been limited in scope and sample size.[8,9] Therefore, we conducted a randomized, phase 2 study with the objective of comparing efficacy and safety between the IP and EP regimens in patients with advanced GEP-NEC.

MATERIALS AND METHODS

Study Design and Participants

The current study was an investigator-initiated, randomized, open-label, phase 2 study that enrolled patients with advanced or recurrent and/or metastatic poorly differentiated GEP-NECs. The pathological findings, obtained either from biopsy or surgical specimens, were reviewed independently (histologic subtype and Ki-67) and the diagnosis confirmed by 2 pathologists. The eligibility criteria were: 1) patients either were chemotherapy-naive or had received adjuvant chemotherapy >6 months before recurrence; 2) patients had measurable disease according to the Response Evaluation Criteria in Solid Tumors (version 1.1); 3) patients were aged 18 to 75 years; 4) patients had an Eastern Cooperative Oncology Group performance status of 0 to 1; 5) patients had a life expectancy ≥3 months; 6) patients had adequate renal function, defined as serum creatinine ≤1.5 times the upper limit of normal (ULN); 7) patients had adequate hepatic function, defined as total and direct bilirubin ≤1.5 times the ULN and alanine aminotransferase and aspartate aminotransferase ≤2.5 the ULN and ≤5 times the ULN within the setting of liver metastases; and 8) patients had adequate bone marrow function, defined as an absolute neutrophil count ≥1500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥9 g/dL. Female patients of childbearing potential were required to have a negative serum or urine pregnancy test result within 7 days before study enrollment, and all fertile patients had to agree to use contraception during the study until 30 days after the end of the study.

The exclusion criteria were: 1) a history of palliative chemotherapy or disease recurrence <6 months from the time of last adjuvant chemotherapy and/or radiotherapy; 2) known hypersensitivity to irinotecan, etoposide, or cisplatin; (3) receipt of surgery within the past 4 weeks before study enrollment; 4) severe, uncontrolled, concurrent diarrhea; 5) concurrent severe infection; 6) severe, uncontrolled medical condition that would affect compliance or obscure the interpretation of toxicity determination or adverse events, including severe liver disease, heart disease, uncontrolled diabetes or hypertension, or pulmonary disease; 7) another previous malignancy diagnosed within the past 5 years except for nonmelanoma skin cancer; and 8) presence of neurological or psychiatric abnormalities that affect cognition.

The current study was approved by the ethics committee of the Peking University School of Oncology and was registered at ClinicalTrials.gov with the identifier NCT03168594. All patients provided written informed consent.

Treatment Regimen

Patients randomly were assigned at a 1:1 ratio to the EP arm or the IP arm. The EP regimen comprised 100 mg/m^2 of etoposide on days 1, 2, and 3 and cisplatin at a dose of 75 mg/m^2 on day 1 of a 21-day cycle. Meanwhile, we used a modified IP regimen comprised of 60 mg/m^2 of irinotecan on days 1 and 8 and cisplatin at a dose of 60 mg/m^2 on day 1 of a 21-day cycle. The 2 regimens were repeated for 6 cycles or until disease progression, patient refusal, or the occurrence of unacceptable toxicity. Patients who achieved an objective response or stable disease after 6 cycles of the IP regimen were given maintenance irinotecan (Fig. 1). Posttreatment follow-up consisted of routine reassessment at 6-week to 8-week intervals.

Efficacy and Safety Assessment

All patients who received at least 1 dose of the study drug were included in the efficacy and safety assessment. The primary endpoint was the objective RR (ORR). Spiral computed tomography (CT) scan or magnetic resonance imaging of the chest, abdomen, pelvis, and/or brain was performed at baseline and assessed every 2 cycles for the evaluation of efficacy according to Response Evaluation Criteria in Solid Tumors (version 1.1). The secondary endpoints were OS, PFS, and toxicity. OS was defined as the length of time from the first treatment until death. PFS was measured from the date of chemotherapy initiation to disease progression. Toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Pretreatment evaluations included complete medical history, physical examination, Karnofsky performance status score, complete blood count, and serum chemistry. Tumor staging using CT scans of the chest and abdomen was required. A bone scan was indicated if the presence of bone metastases was clinically suspected.

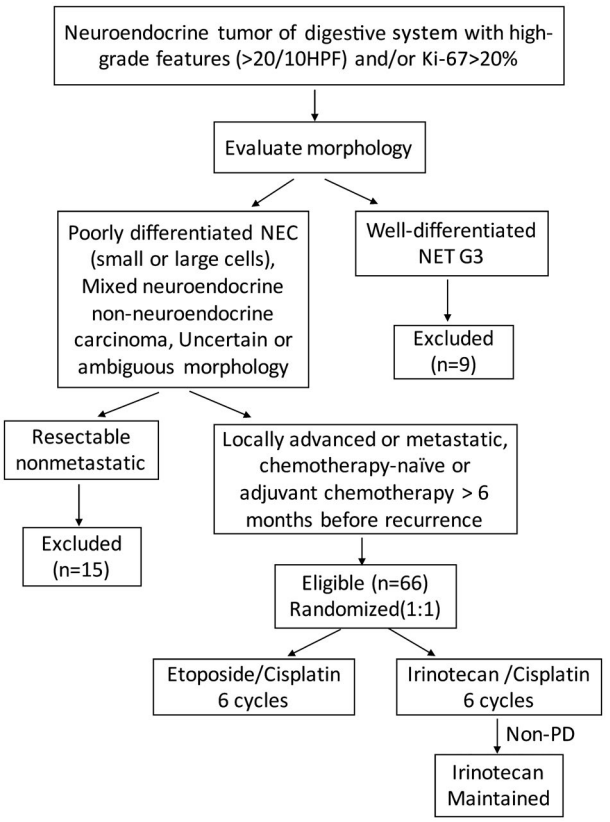

Figure 1. Patient selection and management flowchart. G3 indicates grade 3; HPF, high-power fields; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PD, progressive disease.

Tumor stages were determined according to the American Joint Committee on Cancer 8th staging systems.

Statistical Analysis

For the sample size calculation, a total of 72 patients per arm was required for the study to demonstrate a significant difference (at the 5% level) with a statistical power of 80%. The primary goal was an ORR of 30% for the EP arm and 50% for the IP arm. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. The Fisher exact test was used to compare the patient characteristics, response, and disease control rates, and toxicities between the 2 treatment arms. All statistical analyses were performed using SPSS statistical software (version 25.0; IBM Corporation, Armonk, New York), and 2-sided *P* values <.05 were considered to be statistically significant.

RESULTS

Patients and Treatment

From June 2017 to February 2019, a total of 66 patients with advanced GEP-NEC were enrolled and randomized to either the EP arm or the IP arm. The patients' characteristics were well balanced between the 2 arms (Table 1). The majority of patients were male (69.7%), and the most common primary tumor site was the stomach (20 patients; 30.3%), followed by the esophagus (13 patients; 19.7%), colorectum (11 patients; 16.7%), pancreas (7 patients; 10.6%), duodenum (4 patients; 6.1%), small intestine (3 patients; 4.5%), and unknown site (8 patients; 12.1%). The majority of patients (59 patients; 89.4%) had stage IV or recurrent disease and only 7 patients had locally advanced disease.

TABLE 1. Patient Characteristics

Characteristic	EP Arm N = 33 No. (%)	IP Arm N = 33 No. (%)	*P*
Age, y			.81
<65	18 (54.5)	17 (51.5)	
≥65	15 (45.5)	16 (48.5)	
Sex			.59
Male	22 (66.7)	24 (72.7)	
Female	11 (33.3)	9 (27.3)	
ECOG PS score			.67
0	23 (69.7)	22 (66.7)	
1	10 (30.3)	11 (33.3)	
Primary tumor location			.31
Pancreas	2 (6.1)	5 (15.2)	
Esophagus	10 (30.3)	3 (9.1)	
Stomach	9 (27.3)	11 (33.3)	
Duodenum	1 (3.0)	3 (9.1)	
Small intestine	1 (3.0)	2 (6.1)	
Colorectum	5 (15.2)	6 (18.2)	
CUP	5 (15.2)	3 (9.1)	
Ki-67 index			.64
<55%	2 (6.1)	3 (9.1)	
≥55%	31 (93.9)	30 (90.9)	
Morphology			.38
Small cell	19 (57.6)	13 (39.4)	
Large cell	9 (27.3)	16 (48.5)	
MiNEC	3 (9.1)	2 (6.1)	
Uncertain	2 (6.1)	2 (6.1)	
Stage of disease			.68
III	4 (12.1)	3 (9.1)	
IV	29 (87.9)	30 (90.9)	
Surgery of primary tumor	6 (18.2)	7 (21.2)	.75
No. of metastatic sites			.82
1	12 (36.4)	12 (36.4)	
2	10 (30.3)	12 (36.4)	
>3	11 (33.3)	9 (27.2)	
Metastatic sites			.42
Liver	13 (39.4)	10 (30.3)	
Peritoneal	4 (12.1)	1 (3.0)	
Lung	0 (0)	2 (6.1)	
Brain	2 (6.1)	1 (3.0)	
Bone	3 (9.1)	5 (15.2)	
Lymphatic	23 (69.7)	23 (69.7)	
Other	3 (9.1)	6 (18.2)	

Abbreviations: CUP, carcinoma of unknown primary tumor; ECOG PS, Eastern Cooperative Oncology Group performance status; EP, etoposide and cisplatin; IP, irinotecan and cisplatin; MiNEC, mixed neuroendocrine nonneuroendocrine carcinoma.
Tumor stages were determined according to the American Joint Committee on Cancer 8th staging systems.

Of the 59 patients with metastatic disease, 6 developed disease recurrence after radical surgery, and 7 underwent palliative surgery of the primary tumor. In total, 32 patients (48.5%) had small cell NEC (SCNEC), 25 patients (37.9%) had large cell NEC (LCNEC), 5 patients (7.6%) had mixed neuroendocrine nonneuroendocrine carcinoma (MiNEC), and 4 patients (6.1%) had uncertain or ambiguous morphology. Of the 8 patients with an unknown primary tumor, 5 had SCNEC. Chest CT was performed for every patient at baseline and every 2 cycles for evaluation; no patient was found to have a primary lung tumor.

At the time of analysis, the median number of treatment cycles was 3 for the EP arm and 4 for the IP arm. Eight patients received only 1 cycle (3 patients in the EP arm and 5 patients in the IP arm) due to rapid tumor progression (3 patients) and treatment-related toxicity (2 patients who both developed febrile neutropenia, thrombocytopenia, and diarrhea and 3 patients with a treatment delay of >2 weeks due to toxicity). In total, 11 patients (33.3%) completed the planned 6 cycles of EP chemotherapy and discontinued the treatment. Of patients receiving the IP regimen, 16 patients (48.5%) completed the planned 6 cycles of the regimen; of these, 11 patients went on to receive maintenance irinotecan according to the protocol, and the remaining 5 patients demonstrated disease progression after 6 cycles of IP after second-line treatment. The median maintenance time of irinotecan was 2.8 months (range, 0.7-6.3 months). The RR of the patients who were able to complete 6 cycles of treatment was 72.7% (8 of 11 patients) and 75% (12 of 16 patients), respectively, in EP and IP arms. Table 2 shows the completion of the EP or IP regimen and subsequent treatment.

TABLE 2. Completion of EP and IP Regimens and Subsequent Treatment

	EP Arm N = 33 No. (%)	IP Arm N = 33 No. (%)
No. of treatment cycles		
6 cycles	11 (33.3)	16 (48.5)
5 cycles	1 (3.0)	2 (6.0)
4 cycles	5 (15.2)	5 (15.2)
3 cycles	1 (3.0)	1 (3.0)
2 cycles	12 (36.4)	4 (12.1)
1 cycle	3 (9.1)	5 (15.2)
Ongoing treatment	1 (3.0)	2 (6.0)
Discontinued therapy		
Disease progression	13 (39.4)	8 (24.2)
Adverse events	7 (21.2)	4 (12.1)
Patient refusal	1 (3.0)	3 (9.1)
Second-line therapy		
FOLFOX/CAPOX	0 (0)	3 (9.1)
FOLFIRI	6 (18.2)	0 (0)
Others	6 (18.2)	10 (30.3)
Best supportive care	5 (15.2)	7 (21.2)
Radiotherapy	7 (21.2)	3 (9.1)
TAE/TACE	2 (6.0)	3 (9.1)

Abbreviations: EP, etoposide and cisplatin; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; FOLFOX/CAPOX, 5-fluorouracil, leucovorin and/or capecitabine and oxaliplatin; IP, irinotecan and cisplatin; TACE, transcatheter arterial chemoembolization; TAE, transcatheter embolization.

Efficacy and Safety

The last follow-up date was April 2019. All patients received at least 1 cycle of treatment, and 61 patients were evaluable for tumor response. During the follow-up period, 14 patients, 6 patients, and 11 patients, respectively, achieved a partial response, stable disease, and progressive disease in the EP arm, whereas 14 patients, 12 patients, and 4 patients, respectively, achieved a partial response, stable disease, and progressive disease in the IP arm. In total, 5 patients (2 in the EP arm and 3 in the IP arm) discontinued treatment before the first postbaseline scan and therefore were excluded from the efficacy assessment. The ORRs of the EP arm and the IP arm both were 42.4% (14 of 33 patients). With respect to morphology, the ORRs were 63.2% (12 of 19 patients) and 61.5% (8 of 13 patients) ($P = .61$), respectively, among patients with SCNEC in the EP arm and IP arm, and 14.3% (2 of 14 patients) and 30.0% (6 of 20 patients) ($P = .42$), respectively, in those with non-SCNEC for the EP and IP arms. The EP arm had a lower disease control rate than the IP arm, but the difference was not statistically significant (60.6% [20 of 33 patients] vs 78.7% [26 of 33 patients]; $P = .11$). The median PFS was 6.4 months and 5.8 months, respectively, for the EP and IP arms ($P = .81$), whereas the median OS was 11.3 months and 10.2 months, respectively, for the EP and IP arms ($P = .37$) (Fig. 2).

The main hematological and nonhematological toxicities among all patients are summarized in Table 3. The most common grade 3/4 adverse events were neutropenia, anemia, and diarrhea, whereas the most common grade 1/2 adverse events were nausea, vomiting, alopecia, and fatigue. The incidence of grade 3/4 neutropenia was found to be significantly higher in the EP arm compared with the IP arm (45.4% vs 12.1%; $P = .002$). Nonhematologic toxicities were relatively mild (grade 1/2), and were significantly more frequent in the IP arm compared with the EP arm (54.5% vs 18.2%; $P = .001$). No treatment-related deaths occurred during the study or within 28 days after administration of the last study dose.

DISCUSSION

Chemotherapy has been a cornerstone of treatment for patients with GEP-NEC because of the tumor's histopathologic similarities to SCLC. IP and EP are among

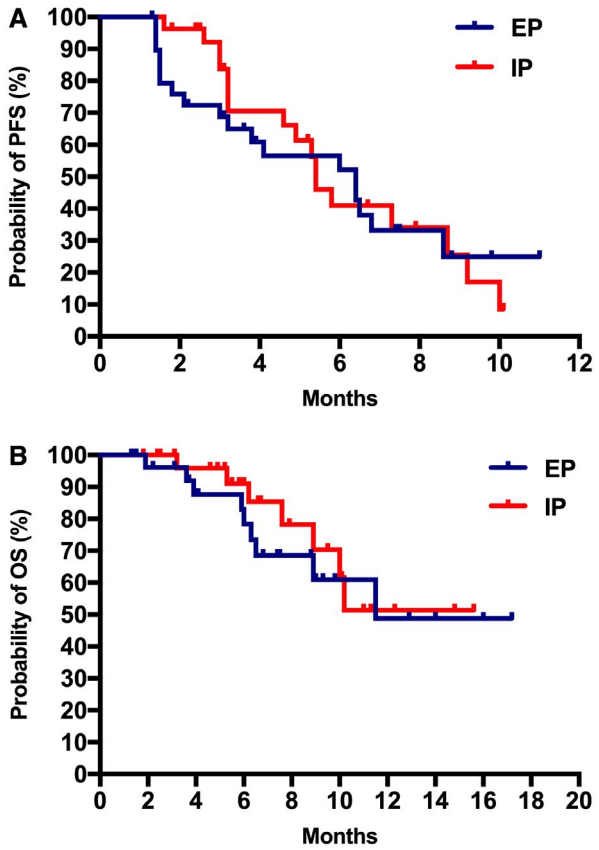

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) according to the treatment arm. Tick marks indicate patients whose data were censored. EP indicates etoposide and cisplatin; IP, irinotecan and cisplatin.

the standard first-line chemotherapy regimens and have comparable antitumor efficacy. However, despite using the same regimen, the RR among patients with extrapulmonary NEC is apparently lower than that of patients diagnosed with its pulmonary counterpart.[10] Furthermore, despite some similar molecular characteristics, disease behaviors and treatment outcomes may differ between GEP-NEC and SCLC.[11] Nevertheless, to the best of our knowledge, there are limited data from randomized studies regarding chemotherapy for patients with advanced GEP-NEC. Moreover, in the 2010 WHO classification,[12] the importance of the Ki-67 index was emphasized in the grading of neuroendocrine neoplasms. In the more recent 2017 WHO classification, histological differentiation has been recognized as being important for the diagnosis of NEC.[13] Thus, it currently is difficult to achieve consensus regarding the optimal standard treatment modality for patients with advanced NEC based on previous reports. To the best of our knowledge, the current study is the first randomized controlled study to compare the efficacy and safety of EP and IP as first-line treatment in patients with advanced GEP-NEC. The primary goal of an ORR of 30% for the EP arm and 50% for the IP arm was not met because there was no significant difference in the ORRs between the EP and IP regimens. Moreover, there was no difference noted with regard to the median PFS and OS between the 2 arms. Because an increase in the number of samples was unable to close the ORR gap of 20% between the 2 arms, the trial was stopped well short of goal accrual.

The ORR in the EP regimen was 42.4%, and the PFS and OS were 6.4 months and 11.3 months, respectively, which is in concordance with those in previous reports. Platinum chemotherapy combined with etoposide in patients with extrapulmonary NEC yielded RRs ranging from 42% to 67% and a median OS between 10 and 15 months.[14,15] However, in what to our knowledge is the largest retrospective study to date (Nordic study), which enrolled 252 patients with advanced GEP-NEC to receive EP or carboplatin and etoposide, the ORR was only 31% and the median PFS and OS were 4 months and 11 months, respectively.[16] However, approximately 47% of the subjects in this Nordic study demonstrated a Ki-67 index of <55% and had been treated before the recent WHO criteria were published in 2017. A recent retrospective analysis reported that the EP regimen had limited efficacy among patients with well-differentiated NEC, but it was effective in those with poorly differentiated NEC.[17] In the current study, all patients had poorly differentiated NEC and therefore the ORR of the EP regimen was relatively higher herein compared with those with grade 3 disease who were selected according to the WHO 2010 criteria in the previous study.

IP is an alternative regimen. A retrospective study that included 50 patients with NEC who were treated with the IP regimen[18] reported an ORR of 50% and a median PFS of 4.8 months. In a previous phase 2 trial, a total of 40 patients with advanced GEP-NEC who received IP as a first-line therapy achieved an ORR of 45.0%, a PFS of 5.7 months, and an OS of 12.9 months.[19] A retrospective Japanese study demonstrated that IP yielded a better response and survival than EP in patients with NEC of the digestive system.[7] However, unequal allocation of patients to the 2 treatment arms may have influenced these findings. In the current study, the ORR in the IP treatment arm was 42.4%, which was lower than in the previous reports. Furthermore, there was no significant difference in ORR noted between the 2 treatment arms.

Morphologically, poorly differentiated NEC encompasses the following histopathological entities: SCNEC,

TABLE 3. Hematologic and Nonhematologic Adverse Events[a] in All Patients Who Received at Least 1 Dose of the Study Drug

Adverse Event	EP Arm N = 33 Grades 1 and 2	IP Arm N = 33 Grades 1 and 2	EP Arm N = 33 Grades 3 and 4	IP Arm N = 33 Grades 3 and 4	*P*
Leukopenia	13 (39.4)	6 (18.2)	7 (21.2)	2 (6.1)	.07
Neutropenia	7 (21.2)	3 (9.1)	12 (36.4)	2 (6.1)	.002
Anemia	3 (9.1)	1 (3.0)	1 (3.0)	0	.31
Thrombocytopenia	2 (6.1)	1 (3.0)	1 (3.0)	1 (3.0)	—
Elevated ALT/AST	2 (6.1)	2 (6.1)	1 (3.0)	0	.31
Nausea	4 (12.1)	14 (42.4)	2 (6.1)	3 (9.1)	.55
Vomiting	2 (6.1)	9 (27.3)	1 (3.0)	1 (3.0)	—
Diarrhea	0	4 (12.1)	0	1 (3.0)	.31
Alopecia	2 (6.1)	0	0	0	—
Fatigue	1 (3.0)	1 (3.0)	2 (6.1)	2 (6.1)	—
Anorexia	4 (12.1)	6 (18.2)	2 (6.1)	3 (9.1)	.55

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EP, etoposide and cisplatin; IP, irinotecan and cisplatin.
[a]Classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

LCNEC, and MiNEC.[20] To our knowledge, small cell carcinoma was the first category described in the lungs, and for this reason, the classic description of SCNEC and LCNEC does not perfectly translate into the GEP tract. Morphological classification in NEC currently is challenging. There still were cases considered to be ambiguous during a morphological review assessment.[21] It is unclear whether SCNEC should be treated differently from non-SCNEC. Currently, the National Comprehensive Cancer Network treatment guidelines suggest using the same approach as with other non–small cell lung cancer tumors to treat pulmonary LCNEC. However, LCNEC and SCNEC have been shown to behave differently and to have significant differences in survival.[22] Although evidence has suggested that GEP-NEC is not a homogenous entity, the European Neuroendocrine Tumor Society guidelines still recommended platinum-based chemotherapy for the treatment of all patients with GEP-NEC.[23] In the current study, SCNEC demonstrated a similar response to both the EP and IP regimens. By contrast, there was a trend toward better efficacy for IP compared with EP in patients with non-SCNEC. Irinotecan has demonstrated activity against various tumor histologies. Marked synergism, a lack of cross-resistance, and a different mechanism of action make the IP combination an attractive regimen. Therefore, IP would be an alternative regimen with acceptable toxicity. In the current study, there was a trend toward an improved response rate in the patients in the non-SCNEC subgroup who were treated using the IP regimen. Further study is required to determine the appropriateness of treating all patients with NEC using the same chemotherapy regimen, and whether different morphologies should be investigated separately.

Myelosuppression was the most frequent toxic effect noted in both treatment arms, but was more common in the EP arm. Meanwhile, there were fewer hematological and greater gastrointestinal toxicities with the IP regimen, a finding that is consistent with previous studies.[5,6,9] It is interesting to note that a previous retrospective study that was conducted to evaluate the efficacy and safety of IP in patients with GEP-NEC reported that the cohort experienced grade 3/4 toxicities such as neutropenia (56.3%), leukopenia (31.2%), diarrhea (12.5%), nausea (6.3%), and vomiting (6.3%).[24] In our previous phase 2 study, the most common toxicities also included grade 3/4 leukopenia and/or neutropenia (60%), nausea and/or vomiting (17.5%), and diarrhea (12.5%) with the combination of irinotecan at a dose of 180 mg/m^2 and cisplatin at a dose of 50 mg/m^2 administered by intravenous infusion on day 1 every 2 weeks.[19] In patients with SCLC, the IP regimen consisted of irinotecan at a dose of 60 mg/m^2 on days 1, 8, and 15 and cisplatin at a dose of 60 mg/m^2 on day 1 every 4 weeks.[5] The Korean group used a slightly different regimen composed of irinotecan at a dose of 65 mg/m^2 on days 1 and 8 and cisplatin at a dose of 70 mg/m^2 on day 1 every 3 weeks.[6] Therefore, in the current study, we referred to the regimen administered in patients with SCLC and modified the dose of the IP, and found that the majority of associated toxicities were milder compared with those reported in previous studies.

Although the current study was a randomized trial, there were many limitations that could have biased the results, including the small patient cohort size and the inclusion of unknown pathology or MiNECs. The rarity of the tumor type is a limiting factor and also resulted in a rather heterogeneous study cohort inclusive of variable morphologies and disease states (recurrent, metastatic,

locally advanced, previously resected, etc). Thus, it was difficult to ascertain whether the conclusions were broadly applicable. Furthermore, the current study was stopped well short of goal accrual, which limited it further. Moreover, the small percentage of the subjects who completed planned therapy was another study limitation.

IP is not inferior to EP, and demonstrated comparable efficacy for patients with poorly differentiated NEC of the digestive system. In addition, both regimens appear to be well tolerated despite their different toxicity profiles. The most common toxicities noted in the current study were myelosuppression in the EP arm and gastrointestinal toxicity in the IP arm.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Panpan Zhang: Writing of the main article and statistical analysis. **Jie Li:** Study design. **Jian Li:** Data collection. **Xiaotian Zhang:** Data collection. **Jun Zhou:** Data collection. **Xicheng Wang:** Data collection. **Zhi Peng:** Data collection. **Lin Shen:** Study design and article revision. **Ming Lu:** Study design and article revision. All authors have read and approved the article.

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