Comparison of Chemotherapeutic Treatment Outcomes of Advanced Extrapulmonary Neuroendocrine Carcinomas and Advanced Small-Cell Lung Carcinoma

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Key Words

Extrapulmonary neuroendocrine carcinoma • Small-cell lung carcinoma • Chemotherapy • Prognosis • Prognostic factor

Abstract

Background: The chemotherapy for small-cell lung carcinoma (SCLC) has been adopted for advanced extrapulmonary neuroendocrine carcinomas (EP-NECs). The aim of this study was to clarify the efficacy of standard SCLC regimens when used to treat EP-NECs and to compare the outcome with that for SCLC. **Methods:** We reviewed the medical records of 136 patients (41 with EP-NEC and 95 with SCLC) who were treated using a platinum-containing regimen for advanced disease between January 2000 and October 2008 at our hospital. **Results:** The primary site of the EP-NEC was the gastrointestinal tract in 18 patients (GI tract group); the liver, biliary tract or pancreas in 16 patients (HBP group), and other sites in 7 patients ('others' group). The response rate in the SCLC patients was 77.8%, and the response rate in the EP-NEC patients was 30.8% (37.5% in the GI tract group, 12.5% in the HBP group, and 57.1% in the 'others' group). The median survival time for

the SCLC patients was 13.6 months, while that for the EP-NEC patients was 9.2 months (14.9 months in the GI tract group, 7.8 months in the HBP group, and 8.9 months in the 'others' group). A multivariate analysis demonstrated that a poor performance status, liver involvement, and the treatment regimen were independent unfavorable prognostic factors.

Conclusion: The response rate and prognosis of the patients with advanced EP-NECs were worse than those of the patients with SCLC in this study. The Eastern Cooperative Oncology Group performance status, liver involvement, and treatment regimen had a larger impact on the prognosis than the primary tumor site, as demonstrated by multivariate analysis.

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Introduction

Neuroendocrine neoplasms are defined as all neoplasms originating from endocrine glands, nerve elements, or from elements of the diffuse neuroendocrine system [1]. The World Health Organization (WHO) has proposed a grading system for neuroendocrine neo-

plasms that divides them into three tiers based on proliferation as follows [2]: (1) neuroendocrine tumor (NET) (G1): mitotic count <2 per 10 high power fields (HPF) and/or a Ki67 index of $\leq 2\%$; (2) NET (G2): mitotic count 2–20 per 10 HPF and/or a Ki67 index of 3–20%, and (3) neuroendocrine carcinoma (NEC): mitotic count >20 per 10 HPF and/or a Ki67 index of >20%. Among these classes, NEC is a poorly differentiated, high-grade malignant neoplasm. The definition of NEC refers to neoplasms previously classified as small-cell carcinoma or poorly differentiated (neuro)endocrine carcinoma (PDNEC). Since the first report of ‘extrapulmonary oat cell carcinoma’ of the mediastinum by Duguid and Kennedy [3] in 1930, extrapulmonary NECs (EP-NECs) have been reported to arise in a variety of organs, such as the gastrointestinal tract, pancreas, head and neck region, or urogenital tract [4–16]. EP-NECs are a fairly rare, heterogeneous disease entity, and no standard treatment has been established [17, 18]. Especially for extended or recurrent EP-NECs, treatment with combined etoposide and cisplatin, which is a representative regimen for the treatment of small-cell lung carcinoma (SCLC), has been mainly adopted [19–21] until now because these tumors share many features, including their immunohistochemical findings and aggressive clinical behavior [8]. However, some cytogenetic analyses have revealed differences between the two entities [6, 14, 22]. Therefore, EP-NECs may differ from SCLC with respect to their sensitivity to anticancer agents or patient outcome [7]. The aim of the present study was to clarify the efficacy of standard SCLC regimens when used for the treatment of advanced EP-NECs and to compare the outcome with that for SCLC. Moreover, we compared the sensitivity to systemic chemotherapy and the patient outcome according to the primary tumor site to identify prognostic factors.

Materials and Methods

Patients and Methods

This study was approved by the Ethics Committee of the National Cancer Center, Japan. The pathology records of the National Cancer Center Hospital, Tokyo, Japan (January 2000 to December 2008) were searched for neuroendocrine neoplasms. In all the patients, a fine-needle biopsy or surgical specimen had been used for the pathological diagnosis. Clinical information was obtained from the patients’ medical records. Patients with EP-NEC or small-cell lung cancer according to the WHO classification [2, 23], chemotherapy-naïve patients with extended or recurrent disease, and patients treated with platinum-based combined chemotherapy [a regimen consisting of cisplatin and etoposide (PE regimen), cisplatin and irinotecan (IP regimen), or carboplatin and

etoposide (CE regimen)] were considered for enrollment. If accurate proliferation fraction, such as Ki67 index or mitotic count, could not be obtained, tumor differentiation was diagnosed morphologically. In such cases, PDNECs according to the WHO 2004 [24] classification were considered as eligible. Patients who were participating in ongoing prospective clinical trials were excluded from the analysis. All the patients underwent computed tomography (CT) examinations to determine the tumor stage. CT scans of the brain or bone scans were also performed mainly in symptomatic patients. Upper and lower gastrointestinal endoscopic examinations were performed in patients with gastrointestinal NECs or unknown primary tumors. An extended NEC stage was defined as the presence of any single or multiple metastases at any distant anatomical site (including non-regional nodes), corresponding to the extended stage of the two-stage system for SCLC that was originally introduced by the Veterans’ Administration Lung Study Group [25]. We investigated the patients’ backgrounds, treatment efficacy, and the patient outcome according to the primary site. Thereafter, we compared the sensitivity to systemic chemotherapy and the patient outcome according to the primary tumor site to identify prognostic factors.

Study Design

The response to chemotherapy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [26]. A response rate was defined as the sum of the complete response rate and the partial response rate. The χ^2 test was used to assess differences in the patient characteristics of the EP-NEC and SCLC groups and the relation between the primary tumor site and the response rate. Overall survival (OS) was calculated from the first day of treatment until the date of death or the last day of the follow-up period. In the univariate analysis, the cumulative survival proportions were calculated using the Kaplan-Meier method [27], and any differences were evaluated using the log-rank test. Only variables that achieved statistical significance in the univariate analysis were subsequently evaluated in the multivariate analysis using Cox’s proportional hazards regression model [28]. A *p* value of <0.05 was considered statistically significant, and all the tests were two-sided. All statistical analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for Windows).

Results

We retrospectively reviewed 981 patients with a pathologically confirmed diagnosis of neuroendocrine neoplasms (511 from extrapulmonary organs and 470 from the lung). Overall, 136 patients (41 with EP-NECs and 95 with SCLC) met the above-described criteria (fig. 1). The patient characteristics are summarized in table 1. The median age of the patients with EP-NECs was 58 years, which was significantly younger than that of the patients with SCLC (67 years). The patients included 26 males (63.4%) with EP-NECs and 75 males (78.9%) with SCLC; while the percentage of male subjects with EP-NECs was

Fig. 1. Study population. The target population of this study was patients with extended or recurrent extrapulmonary PDNECs or small-cell carcinoma who had been treated with chemotherapy (PE, IP or CE regimen) at our institute.

lower than that of male subjects with SCLC, the difference was not statistically significant. The majority of patients in both groups had a good performance status: 97.6% of the patients with EP-NECs and 90.5% of the patients with SCLC had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Brain and lymph node metastases were observed more frequently among patients with SCLC than among those with EP-NECs ($p < 0.01$ and $p < 0.01$, respectively), whereas liver involvement was observed significantly more often among patients with EP-NECs than among those with SCLC ($p < 0.01$). The major primary sites of EP-NECs were the stomach in 10 patients, followed by the pancreas in 9 patients and the esophagus in 8 patients (table 2). We divided the patients with EP-NECs into three groups according to the primary tumor sites: the gastrointestinal tract group (GI tract group), comprising 43.9% of the EP-NECs; the liver, biliary tract or pancreas group (HBP group), comprising 39.0% of the EP-NECs, and the 'others' group (prostate, thymus, bladder, and unknown primary), comprising 17.1% of the EP-NECs. Patient characteristics are summarized in table 1. Overall, systemic chemotherapy was performed according to the PE regimen in 31 patients, the IP regimen in 70 patients, and the CE regimen in 35 patients (table 3). The tumor

responses to chemotherapy are shown in table 4. The response rate was significantly higher in the SCLC group (77.8%) than in the EP-NEC group (30.8%; $p < 0.01$). Of the patients with EP-NECs, the response rate in the HBP group (12.5%) was significantly lower than that of the 'others' group (57.1%; $p = 0.025$) and tended to be lower than that in the GI group (37.5%; $p = 0.10$). The median survival time (MST) of the patients with EP-NECs was 9.2 months and had a tendency to be worse than that of SCLC patients with 13.6 months, but the difference was not significant ($p = 0.067$; fig. 2). The 1-year survival rate (61.1 vs. 38.6%) was better for the patients with SCLC than EP-NECs. And a few patients (11.8%) with SCLC but no patients with EP-NECs survived longer than 3 years. The MSTs of patients treated with an IP regimen, PE regimen, and CE regimen are shown in table 5. Of the patients with EP-NECs, the MSTs of the patients in the GI tract group, the HBP group, and the 'others' group were 14.9, 7.8, and 8.9 months, respectively ($p < 0.01$; fig. 3). The following 8 of the 15 pretreatment variables that were evaluated were identified as being significantly associated with the survival time in univariate analyses (table 6): ECOG PS ($p < 0.01$), primary site ($p < 0.01$), neuron-specific enolase (NSE; $p = 0.025$), hemoglobin ($p = 0.029$), albumin ($p < 0.01$), alkaline phosphatase ($p = 0.030$), liv-

Table 1. Clinical characteristics of the patients

	EP-NECs				SCLC	p value
	Total	GI tract group	HBP group	'Others' group		
Patients	41	18	16	7	95	
Age, years						<0.01*
Median	58	63.5	46.5	59	67	
Range	27–79	27–79	30–69	33–84	43–84	
Gender, n (%)						0.057**
Male	26 (63)	15 (83)	8 (50)	3 (43)	75 (79)	
Female	15 (37)	3 (17)	8 (50)	4 (57)	20 (21)	
EGOG PS, n (%)						0.28**
0	12 (29)	4 (22)	4 (25)	4 (57)	21 (21)	
1	28 (68)	14 (78)	11 (69)	3 (43)	65 (68)	
2	1 (2)	0	1 (6)	0	9 (9)	
NSE, ng/ml						0.050*
Median	43.8	34.2	127.7	14.6	57.2	
Range	7.5–1,930	9.2–210.5	20.7–1930	7.5–571.0	5.5–1,158	
ProGRP, pg/ml						0.69*
Median	43.0	47.9	31.3	48.9	668.4	
Range	5.3–63,090	5.3–13,810	11.9–63,090	21.2–117.1	18.3–40,550	
Metastatic site, n (%)						
Liver	30 (73)	14 (78)	13 (81)	3 (43)	21 (22)	<0.01**
Brain	2 (5)	1 (6)	0	1 (14)	27 (28)	<0.01**
Bone	4 (10)	1 (6)	1 (6)	2 (29)	22 (23)	0.068**
Lung	5 (12)	1 (6)	3 (19)	1 (14)	–	–
Lymph node	21 (51)	13 (72)	5 (31)	0	76 (80)	<0.01**

ProGRP = Pro-gastrin-releasing peptide. * Student's t test, ** χ^2 test.

Fig. 2. Kaplan-Meier plot of OS. The MST of the patients with EP-NECs was 9.2 months and had a tendency to be shorter than that of patients with SCLC, which was 13.6 months. * log-rank test.**Table 2.** Primary tumor site of the patients with EP-NECs

GI tract group	
Stomach	10
Esophagus	8
HBP group	
Pancreas	9
Gallbladder	4
Liver	3
'Others' group	
Thymus	2
Prostate	2
Bladder	2
CUP	2

CUP = Carcinoma of unknown primary site.

Table 3. Chemotherapy regimens

	EP-NECs				SCLC	Total
	Total	GI tract	HBP	Others		
CDDP + VP-16	18	1	16	1	13	31
CDDP + CPT-11	22	17	0	5	48	70
CBDCA + VP-16	1	0	0	1	34	35
Total	41	18	16	7	104	136

CDDP = Cisplatin; VP-16 = etoposide; CPT-11 = irinotecan; CBDCA = carboplatin.

Table 4. Tumor responses

	EP-NECs				SCLC
	Total	GI tract	HBP	Others	
Complete response	1	0	0	1	5
Partial response	11	6	2	3	72
Stable disease	17	6	9	2	7
Progressive disease	10	4	5	1	48
Not evaluable	2	2	0	0	6
Response rate	30.8%	37.5%	12.5%	57.1%	77.8%
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="border-top: 1px solid black; width: 150px; margin: 0 auto;"></div> <div style="text-align: center;">p = 0.10*</div> <div style="border-top: 1px solid black; width: 150px; margin: 0 auto;"></div> <div style="text-align: center;">p = 0.025*</div> </div> <div style="text-align: center; margin-top: 5px;">p < 0.01*</div>					(RECIST version 1.0)

* χ^2 test.

Table 5. The MSTs of the patients treated with IP regimen, PE regimen, and CE regimen

	EP-NECs			SCLC			Total		
	n	MST		n	MST		n	MST	
CDDP + VP-16	18	7.3	] p = 0.001*	13	12.4	] p = 0.023*	31	8.9	] p < 0.001*
CDDP + CPT-11	22	14.9		48	16.6		70	16.6	
CBDCA + VP-16	1	16.9		34	9.3		35	9.3	

CDDP = Cisplatin; VP-16 = etoposide; CPT-11 = irinotecan; CBDCA = carboplatin. * log-rank test.

Table 6. Prognostic factors (univariate analysis)

	n	Median OS $\pm$ SE months	p*
Age			
≥ 64 years	66	12.5 $\pm$ 0.97	0.66
< 64 years	70	12.9 $\pm$ 2.07	
Sex			
Male	101	12.4 $\pm$ 0.99	0.74
Female	35	12.9 $\pm$ 1.34	
ECOG PS			
0–1	126	13.5 $\pm$ 1.64	< 0.01
2–3	10	5.1 $\pm$ 3.02	
Primary site			
Lung	95	13.6 $\pm$ 0.33	< 0.01
GI tract	18	14.9 $\pm$ 8.03	
HBP	16	7.8 $\pm$ 1.49	
Others	7	8.9 $\pm$ 3.52	
NSE			
≥ 15 ng/ml	118	12.1 $\pm$ 1.55	0.025
< 15 ng/ml	18	26.2 $\pm$ 5.05	
ProGRP			
≥ 45 pg/ml	97	13.3 $\pm$ 1.35	0.83
< 45 pg/ml	39	12.4 $\pm$ 1.42	
Hb			
≥ 12 g/dl	85	13.7 $\pm$ 0.40	0.029
< 12 g/dl	51	10.3 $\pm$ 1.96	
CRP			
≥ 0.4 mg/dl	89	11.3 $\pm$ 1.69	0.056
< 0.4 mg/dl	47	14.9 $\pm$ 1.82	
Alb			
≥ 3.7 g/dl	72	14.6 $\pm$ 1.40	< 0.01
< 3.7 g/dl	64	9.3 $\pm$ 0.43	
ALP			
≥ 360 IU/l	37	9.2 $\pm$ 0.68	0.030
< 360 IU/l	99	13.8 $\pm$ 0.88	
LDH			
≥ 230 IU/l	103	11.6 $\pm$ 1.86	0.058
< 230 IU/l	33	18.0 $\pm$ 5.54	
Brain metastases			
Presence	29	12.4 $\pm$ 0.55	0.66
Absence	107	13.6 $\pm$ 0.97	
Bone metastases			
Presence	26	10.4 $\pm$ 3.72	0.078
Absence	110	13.6 $\pm$ 0.36	
Liver metastases			
Presence	51	9.1 $\pm$ 0.35	< 0.01
Absence	85	14.1 $\pm$ 1.46	
Regimen			
CDDP + VP-16	31	8.9 $\pm$ 0.66	< 0.01
CBDCA + VP-16	35	9.3 $\pm$ 1.45	
CDDP + CPT-11	70	16.6 $\pm$ 4.38	

ProGRP = Pro-gastrin-releasing peptide; Hb = hemoglobin; CRP = C-reactive peptide; Alb = albumin; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; CDDP = cisplatin; VP-16 = etoposide; CBDCA = carboplatin; CPT-11 = irinotecan.
* log-rank test.

Fig. 3. Kaplan-Meier curves of OS of the patients with EP-NECs. The MSTs of the patients in the GI tract group, the HBP group, and the 'others' group were 14.9, 7.8, and 8.9 months, respectively. The HBP group had the worst prognosis. * log-rank test.

er involvement ($p < 0.01$), and chemotherapy regimen ($p < 0.01$). Only 3 of the above factors were identified as independent unfavorable prognostic factors in a multivariate Cox regression model: an ECOG PS of 2 or 3 (hazard ratio 3.786; $p < 0.01$), liver involvement (hazard ratio 1.943; $p = 0.013$), and the PE regimen (hazard ratio compared with the IP regimen 1.990; $p = 0.032$; table 7).

Discussion

The definition of NET has been confused for a long time, and the clinical and pathologic features of NETs have been described by many investigators, with most studies focusing on subsets of tumors restricted to one organ or organ system. Site-longitudinal grading, staging, and classification systems have been developed by the WHO [2, 23] and the European Neuroendocrine Tumor Society (ENETS) [29, 30]. Among the parameters of those classification systems, the proliferative index has emerged as a fundamental grading characteristic that now appears in most major schemata. Within these schemata, NECs represent the highest grade of malignancy, and patients with these tumor types have the worst outcome among all patients with neuroendocrine neoplasms [31, 32]. Therefore, the development of an effective therapy for this disease entity is essential.

Systemic chemotherapy for patients with EP-NECs has been conducted according to the regimens used for

Table 7. Prognostic factors (multivariate analysis)

	Hazard ratio (95% CI)	p*
ECOG PS		
2–3	3.786 (1.736–8.259)	<0.01
Primary site		
Lung		
GI tract	1.061 (0.531–2.121)	0.87
HBP	1.390 (0.593–3.255)	0.45
Others	1.364 (0.534–3.480)	0.52
NSE		
≥15 ng/ml	1.480 (0.782–2.803)	0.23
Hb		
<12 g/dl	1.144 (0.740–1.768)	0.55
Alb		
<3.7 g/dl	1.381 (0.890–2.144)	0.15
ALP		
<360 IU/l	1.189 (0.682–2.075)	0.54
Liver involvement		
Presence	1.943 (1.146–3.295)	0.014
Regimen		
CDDP + CPT-11		
CDDP + VP-16	1.990 (1.062–3.731)	0.032
CBDCA + VP-16	1.487 (0.873–2.532)	0.14

Hb = Hemoglobin; Alb = albumin; ALP = alkaline phosphatase; CDDP = cisplatin; CPT-11 = irinotecan; VP-16 = etoposide; CBDCA = carboplatin. * Cox proportional hazards model.

SCLC; however, little is known about treatment efficacy because of the rareness of these cases, unlike SCLC (which accounts for about 20% of all lung cancers). Consequently, we decided to conduct the present investigation. In an attempt to unify the therapeutic procedures among unified patients, the candidates for enrollment were rigidly restricted to patients with pathologically confirmed EP-NECs and SCLC, extended or recurrent disease, and who had been treated with the PE, IP, or CE regimen. The PE or IP regimens are presently considered to be the standard treatment regimens for patients with extended SCLC [33–35]. The CE regimen has been reported to have a similar efficacy to the PE regimen among patients with SCLC and can be considered as an alternative treatment regimen [36].

The first aim of this study was to clarify the efficacy of standard SCLC regimens when used to treat advanced EP-NECs and to compare the treatment outcome with that for SCLC. Our study showed that the response rate of the patients with EP-NECs was lower than that of the patients with SCLC. The objective response rate to platinum-based chemotherapy was 77.8% for the patients with

SCLC, and the MST in the present study was 13.6 months, which was similar to previously reported survival times [33, 34, 36]. On the other hand, the efficacy of such regimens against EP-NECs seemed to be worse in the present study, with a response rate of 31.7% compared with 33–66.7% in previous reports [5, 7, 10, 20, 21]. Although the reason for the difference in the treatment efficacies was unknown, possible reasons include the differences in the criteria used to evaluate response and the relatively small number of patients. Additionally, the response rates of EP-NECs with different primary sites were significantly different, with the HBP group showing the lowest response rate. This finding also disagreed with Brenner et al.'s [5] report, which showed no differences in the response to chemotherapy among the different anatomical locations. The patients with EP-NECs tended to have unfavorable outcomes compared with the patients with SCLC in our study. Some reports have shown that the OS of patients with EP-NECs was better than that of patients with SCLC [7, 16]. In the present study, the most common primary sites of the EP-NECs were the stomach, pancreas, and esophagus. On the other hand, relatively few patients had tumors arising in the reproductive tract, breast, or head and neck region, which have been reported to be associated with a better prognosis [4, 9–12]. At our institution, genitourinary EP-NECs tend to be resected, and head and neck EP-NECs are often treated using chemoradiotherapy. In other words, the outcomes of the patients in a particular study might depend on the ratio of the primary sites. Moreover, an interesting finding in the present study was that although liver involvement was identified as a prognostic factor in a multivariate analysis, the primary site was not a prognostic factor. In fact, liver metastasis is a well-documented poor prognostic factor in patients with NETs [22, 37–40]. Actually, 73% of the EP-NECs exhibited liver involvement in the present study, whereas only 22% of the SCLCs exhibited liver involvement.

Another interesting point of the present study is that the IP regimen was associated with a significantly more favorable outcome than the PE regimen in the multivariate analysis. When the outcome of the SCLC patients was examined according to the chemotherapeutic regimen that was used, the MST associated with the IP regimen was 16.6 months, which was significantly longer than that associated with the PE regimen (12.4 months) or the CE regimen (9.3 months) ($p = 0.023$ and $p = 0.023$, respectively; table 5). These results agree with those of a Japanese report by Noda et al. [35]. A similar trend was observed among patients with EP-NECs in our study.

However, this result should be interpreted with caution because of the bias introduced by the different treatment policies with regard to the selection of chemotherapeutic regimens among the divisions of our institute. For example, all the patients in the HBP group were treated using the PE regimen, whereas a large proportion of the patients in the GI and 'others' groups were treated using the IP regimen (table 3).

The objectives of this study included not only patients with 'extrapulmonary small-cell carcinoma' but also those with 'EP-NEC diagnosed based on a high Ki67 index or high mitotic count without small-cell morphological features; NEC other than small-cell carcinoma'. It is possible that 'NEC other than small-cell carcinoma' may be biologically and clinically different from small-cell carcinoma, and these differences could influence the treatment outcomes of NEC in this study. However, although the terms 'small-cell carcinoma' and 'large-cell carcinoma' were specified in the WHO 2010 classification, no definite indicators distinguishing 'NEC other than small-cell carcinoma' from 'small-cell carcinoma' exist. Therefore, we refrained from comparing them in this study. Additionally, some prognostic factors, such as the Ki67 index, mitotic count or degree of necrosis, may also influence the treatment outcomes. Because information regarding these factors could not be obtained for all the patients in this study and because our main purpose in this study was to compare the clinical outcomes ac-

cording to the primary tumor site, we did not evaluate the chemosensitivity or the patient outcome according to these factors. Nevertheless, these points are very important clinical questions and should be examined in future studies.

Another limitation of this study was its retrospective nature, and a prospective trial with a large number of patients treated using the same chemotherapeutic regimen is needed to confirm our findings.

In conclusion, the response rate and prognosis of patients with extended or recurrent EP-NECs, especially those originating in the liver, biliary tract, or pancreas, were worse than those of the patients with SCLC in this study. The ECOG PS, liver involvement, and treatment regimen had a larger impact on the prognosis than the primary tumor site, as demonstrated by multivariate analysis.

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Disclosure Statement

The authors have no conflicts of interest.

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