Efficacy of 2nd-line chemotherapy in patients with poorly differentiated, high grade extrapulmonary neuroendocrine carcinoma (PD NEC)

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Abstract (Click)

- Standard 1st-line therapy for poorly differentiated neuroendocrine carcinoma is a platinum-etoposide doublet[1], however scant data exists to guide 2nd line therapy
- Second-line regimens for small cell lung cancer are often used, though NEC is pathogenetically distinct from SCLC despite morphological similarities[2]
- We performed a retrospective analysis of all patients at Mayo Clinic treated with 2nd-line regimens for PD NEC
- Inclusion criteria were 1st-line treatment with platinum-etoposide, and subsequent 2nd-line treatment
- Primary end-points were overall survival (OS) and progression-free survival (PFS) from initiation of 2nd-line therapy; secondary end-points included OS and PFS from 1st-line regimens
- 64 patients were included. The median OS from initiation of 2nd-line therapy for all regimens was 6.2 months [95% CI 4.9–8.9]
- No 2nd-line regimen showed a statistically significant difference in OS or PFS, though irinotecan-containing regimens had the longest OS (7.8 months [3.3–14.8]) and paclitaxel-containing regimens (without topotecan) had the longest PFS (2.7 months [1.3–6.4]).

Conclusion

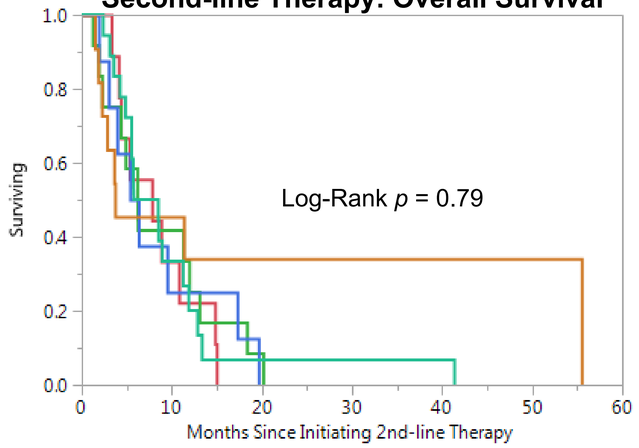
- The efficacy of current 2nd-line therapy in PD NEC is poor.
- No 2nd-line regimen showed statistically significant superiority.
- Cisplatin was associated with a longer OS regardless of 2nd-line regimen or age.
- However, unmeasured confounders such as performance status or comorbidities may explain some of this effect.

Methods

- Retrospective analysis
- Pathologic confirmation of extrapulmonary high grade, PD NEC
- First-line therapy with platinum-etoposide
- End-points: PFS and OS, of 2nd-line regimens as well as for 1st-line regimens
- Regimens (2nd-line): irinotecan, paclitaxel, paclitaxel+topotecan, temozolomide, topotecan
- Regimens (1st-line): carboplatin-etoposide, cisplatin-etoposide
- Progression was assessed by radiologist interpretation of disease progression

Results (Click)

Second-line Therapy: Overall Survival



Therapy	Median OS (m)	95% CI
irinotecan	7.8	3.3 - 14.8
paclitaxel	6.2	1.9 - 13.1
paclitaxel + topo	5.8	1.9 - 17.2
temozolomide	3.7	1.8 - 55.5
topotecan	7.1	4.9 - 11.3
Combined	**6.2**	**4.9 - 8.9**

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Abstract

Background
A platinum/etoposide doublet is standard 1st-line therapy for PD NEC, however evidence to guide treatment beyond 1st-line regimens is lacking. Second-line small cell lung cancer (SCLC) regimens are commonly used, but despite morphological similarities, extrapulmonary PD NEC is genetically distinct from SCLC. This study aimed to evaluate the efficacy of 2nd-line regimens in PD NEC.

Methods
We performed a retrospective analysis of patients treated with 2nd-line chemotherapy for PD NEC. Inclusion criteria were previous 1st-line therapy with platinum/etoposide, extrapulmonary PD NEC, and follow-up data. The primary end points were overall survival (OS) and progression-free survival (PFS) following 2nd-line therapy. Secondary end-points included OS and PFS from 1st-line therapy.

Results
Sixty-four patients were included. The median OS from initiation of 2nd-line therapy for all regimens was 6.2 months [95% CI 4.9–8.9]. The median PFS was 2.3 months [95% CI 2.0–3.2]. No 2nd-line regimen showed a statistically significant difference in OS or PFS, though irinotecan-containing regimens had the longest OS (7.8 months [3.3–14.8]) and paclitaxel-containing regimens (without topotecan) had the longest PFS (2.7 months [1.3–6.4]). Multiple-agent regimens showed a nonsignificant increase in both OS (6.2 months [3.9–10.8]) and PFS (2.3 months [1.8–4.6]) compared to singlets (OS 5.8 months [4.9–11.3]; PFS 2.2 months [1.4–4.1]). Tumors of unknown primary site had the longest PFS from 2nd-line, but this was nonsignificant. There was a significant increase in OS for cisplatin 1st-line regimens compared to carboplatin (17.0 months [12.7–22.6] vs 11.7 months [8.0–14.0]). These patients were younger (median age 54 vs 63), but the effect persisted when controlling for age.

Conclusions
The efficacy of current 2nd-line therapy in PD NEC is poor. No 2nd-line regimen showed statistically significant superiority. Cisplatin was associated with a longer OS regardless of 2nd-line regimen or age. However, unmeasured confounders such as performance status or comorbidities may explain some of this effect.

Results

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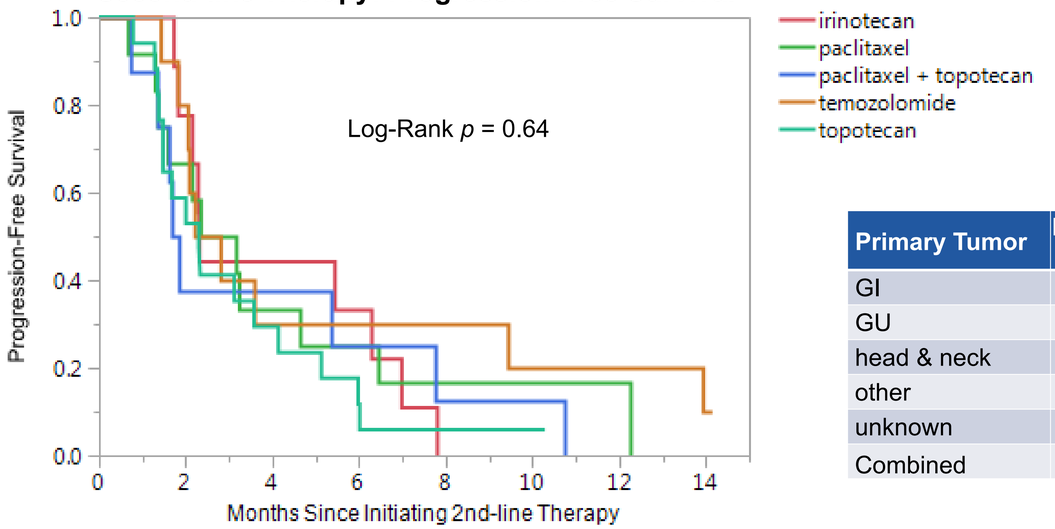
Table 1. Patient characteristics

	Number of patients (n = 64)	%
Age (years)		
Median	57	
Range	21 - 86	
Sex		
Male	42	66
Female	22	34
Primary tumor		
Gastrointestinal	36	56
Genitourinary	9	14
Head & neck	8	13
Unknown	9	14
Other	2	3
Second-line		
Topotecan	18	28
Paclitaxel	12	19
Temozolomide	12	19
Irinotecan	9	14
Paclitaxel + topotecan	8	12
Other	5	8
First-line		
Cisplatin-etoposide	42	67
Carboplatin-etoposide	21	33
Second-line regimen type		
Singlet	27	42
Multiplet*	37	58

* Multiplets included FOLFIRI, FOLFIRINOX, platinum + listed agent, temozolomide + capecitabine

Second-line Therapy: Progression-Free Survival



Primary Tumor	Median OS (m)	95% CI	Median PFS (m)	95% CI
GI	6.3	4.4 - 10.8	2.3	1.8 - 5.4
GU	3.9	1.3 - 11.9	1.7	0.7 - 5.4
head & neck	8.7	4.1 - 12.9	2.1	1.3 - 2.3
other	15.1	10.6 - 19.6	6.1	1.4 - 10.7
unknown	11.3	1.4 - 18.4	3.6	1.4 - 13.9
Combined	6.3	5.3 - 10.6	2.3	2.0 - 3.2

Therapy	Median PFS (m)	95% CI
irinotecan	2.3	1.7 - 7.0
paclitaxel	2.7	1.3 - 6.4
paclitaxel + topo	1.8	0.7 - 7.8
temozolomide	2.5	1.4 - 9.4
topotecan	2.3	1.4 - 4.1
Combined	2.3	2.0 - 3.2

Regimen Type	Median OS (m)	95% CI	Median PFS (m)	95% CI
Singlet	5.8	4.9 - 11.3	2.2	1.4 - 4.1
Multiplet	6.2	3.9 - 10.8	2.3	1.8 - 4.6

Results

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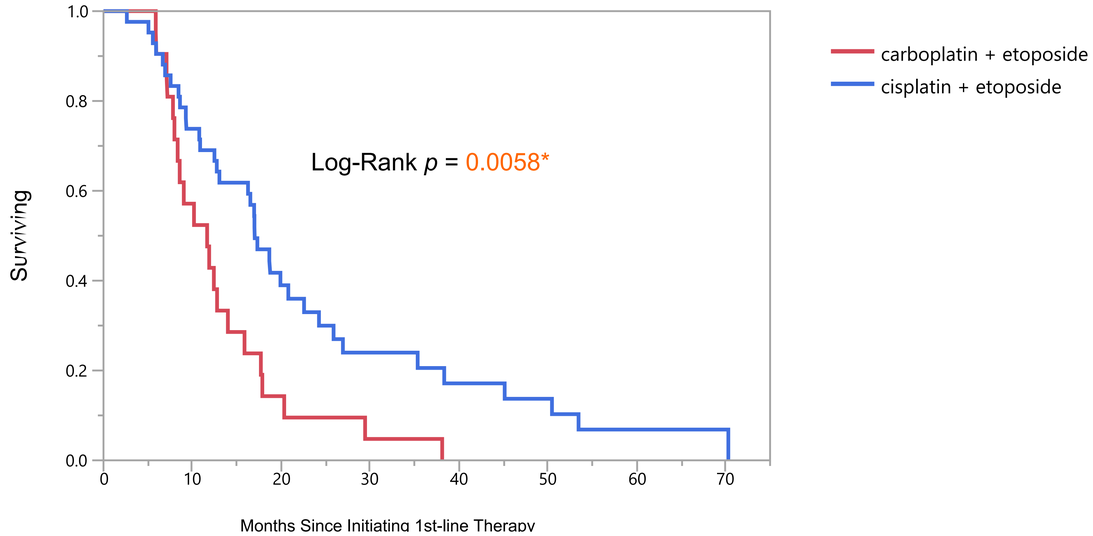
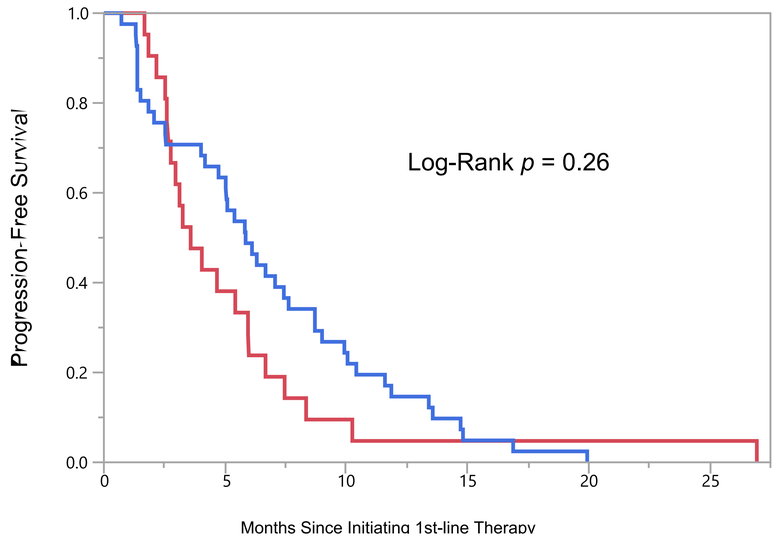
First-line Therapy: Overall Survival



First-line Therapy: Progression-Free Survival



1st-line Therapy	Median OS (m)	95% CI	Median PFS (m)	95% CI
Cisplatin-etoposide	17.0	12.7 - 22.6	5.8	4.2 - 7.6
Carboplatin-etoposide	11.7	8.0 - 14.0	3.6	2.7 - 5.9

* difference remained significant when adjusting for age and 2nd-line regimen with proportional hazards model

References

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1. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS Consensus Guidelines for the Diagnosis and Management of Poorly Differentiated (High-Grade) Extrapulmonary Neuroendocrine Carcinomas. Pancreas. 2010;39(6):799-800. doi:10.1097/MPA.0b013e3181ebb56f.

2. Bergsland EK, Roy R, Stephens P, Ross JS, Bailey M, Olshen A. Genomic profiling to distinguish poorly differentiated neuroendocrine carcinomas arising in different sites. Journal of Clinical Oncology. 2016;34(15_suppl):4020-4020.