Ki-67 proliferative index predicts response to chemotherapy and survival in 252 patients with high-grade gastrointestinal neuroendocrine carcinoma (WHO G3). The Nordic NEC study

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Background

Gastrointestinal high-grade neuroendocrine carcinoma (GI-NEC) account for 35-55% of all extra-pulmonary NEC. Gastrointestinal (GI-NEC) are classified as G3 neuroendocrine tumors in the 2010 WHO classification with a proliferation index Ki-67 > 20%. Many cases have been incorporated in the general neuroendocrine tumor group and other cases frequently misdiagnosed as poorly differentiated adenocarcinoma. GI-NEC are often metastatic at the time of diagnosis, have an aggressive clinical behavior with a poor prognosis. Treatment of GI-NEC patients remain a challenge for the clinician, as there is a lack of epidemiological, clinical and treatment data for these patients.

Methods

Patients were identified at 12 Nordic University Hospitals. Inclusion criteria for study entrance were: histological confirmed diagnosis of a high-grade neuroendocrine carcinoma (Ki-67>20%) with a gastrointestinal primary or an unknown primary (CUP) predominantly with GI metastases and metastatic or not curable locally advanced disease diagnosed between January 2000 and April 2009. Data regarding patient and tumor characteristics, treatment and survival were registered retrospectively. The best cut-off value for Ki-67 regarding response rate was computed using a ROC-analysis.

Results

Palliative chemotherapy was given to 252 patients, median survival was 11 months. Response rate to 1st-line chemotherapy was 31%, 33% had stable disease.

Ki-67<55% was by ROC analyses the best cut-off value concerning correlation to response rate of first-line treatment. Response rate to platinum-based chemotherapy was lower in patients with Ki-67<55% (14% vs.44%, p<0.001). Response rate for 84 patients given 2nd-line chemotherapy was 18%, whereas 33% achieved SD.

The most important negative prognostic factors for survival were poor performance status, primary colorectal tumors, and elevated baseline platelets or lactate dehydrogenase (LDH) levels. Patients with Ki-67<55% had longer median survival (15 months) than patients with Ki-67>55% (10 months) (p<0.001).

Results

Survival and response rates did not differ between the different platinum chemotherapy schedules (cisplatin- vs. carboplatin-based) or morphology subtypes.

Patient characteristics	Chemotherapy treated patients
	N (%)
Total number	252
Treatment period	
2000-2004	67 (79%)
2005-2009	185 (84%)
Median age	58 (24-82)
Performance status	
0	79 (32%)
1	128 (51%)
2	38 (15%)
3-4	5 (2%)
Sex (Male)	124 (49%)
Primary tumor	
Esophageal	9 (4%)
Gastric	16 (6%)
Pancreatic	65 (26%)
Colonic	48 (19%)
Rectal	18 (7%)
CUP	78 (31%)
Other GI	18 (7%)
Primary tumor resected	71 (28%)
Location of metastases	
Liver	173 (69%)
Lymph nodes	165 (66%)
Lung	37 (15%)
Bone	41 (16%)
Brain	8 (3%)
Other	65 (26%)
Small cell morphology	101 (43%)
Non-small cell morphology	134 (57%)
Ki- 67	
< 55%	115 (46%)
≥ 55%	133 (54%)

Response rate and survival according to baseline factors and chemotherapy schedule (n=252)

	PR/CR	SD	PD	PFS (95% CI)	OS (95% CI)
All patients	31%	33%	36%		11 m (9.4-12.6)
Location of primary					
Esophagus	44%	11%	45%	3 m (1.7-4.3)	14 m (2.3-25.7)
Gastric	50%	13%	37%	5 m (3.7-6.3)	11 m (7.1-14.9)
Pancreatic	30%	40%	30%	5 m (3.8-6.2)	15 m (10.3-19.7)
Colon	16%	28%	56%	3 m (2.1-3.9)	8 m (6.0-9.9)
Rectum	23%	53%	24%	4 m (3.1-4.9)	10 m (7.9-12.1)
CUP	37%	31%	32%	4 m (2.8-5.2)	11 m (8.4-13.6)
Performance status					
0	34%	40%	26%	5 m (3.5-6.5)	18 m (14.1-21.9)
1	33%	33%	34%	5 m (3.9-6.1)	12 m (10.3-13.7)
2	23%	16%	61%	2 m (1.1-2.9)	5 m (3.5-6.5)
Ki-67					
<55%	16%	45%	39%	4 m (3.2-4.8)	15 m (10.7-19.2)
≥55%	43%	23%	34%	5 m (4.1-5.9)	10 m (8.6-11.3)

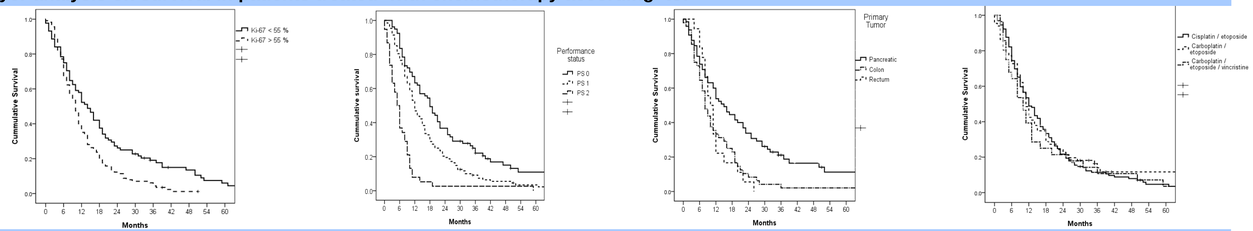
	Cisplatin/ etoposide n=129	Carboplatin/ etoposide n=67	Carboplatin/ etoposide/ vincristine n=28
No of cycles (median, range)	4 (1-15)	5 (1-10)	4 (1-8)
Response rate			
CR	2 %	2 %	0 %
PR	29 %	28 %	44 %
SD	37 %	32 %	24 %
PD	32 %	38 %	32 %
PFS (median, 95% CI)	4 m (3.1-5.0)	4 m (2.6-5.4)	4 m (3.3-4.7)
OS (median, 95% CI)	12 m (9.3-14.6)	11 m (9.2-12.8)	10 m (6.3-13.7)

Use of carboplatin was usually due to center policy

Cox regression for survival in patients treated with chemotherapy. Final model (n=170)

	OR (95%CI)	p-value
Performance status		<0.001
0	0.24 (0.14-0.42)	
1	0.42 (0.25-0.71)	
2	1	
Primary tumor		0.007
Esophageal	1.29 (0.45-3.66)	
Gastric	0.37 (0.14-0.97)	
Pancreatic	0.81 (0.36-1.83)	
Colonic	1.78 (0.83-3.86)	
Rectal	1.24 (0.52-2.99)	
CUP	0.96 (0.45-2.04)	
Other	1	
Platelets < 400 x 10^9	0.47 (0.31-0.72)	<0.001
Lactate dehydrogenase		0.006
Normal	0.50 (0.32-0.78)	
>UNL-2 UNL	0.78 (0.49-1.23)	
> 2 UNL	1	

Kaplan-Meyer analysis on survival in patients treated with chemotherapy according to:



Ki-67 index | **Performance status** | **Location of primary tumor** | **Chemotherapy schedule**

Conclusions

Advanced GI-NEC patients with a Ki-67<55% are less responsive to platinum-based chemotherapy, but have a longer survival than patients with a higher Ki-67.

Poor performance status, colorectal primary and elevated platelets and lactate dehydrogenase levels were the most important negative prognostic factors for survival in chemotherapy treated patients in this large retrospective study.

Carboplatin based chemotherapy do not differ in response rate or survival compared to cisplatin-based chemotherapy.

Our data indicate that it might not be correct to consider all GI-NEC as one single disease entity .

A study by the Nordic Neuroendocrine Tumor Group (NNTG)