Systemic treatment outcomes for neuroendocrine tumour (NET) patients in the Auckland Region:

Preliminary analysis of the NETwork Registry

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AIM

(1) To pilot extraction of clinical data from the Neuroendocrine Tumour Registry

(2) A retrospective analysis of responses to systemic chemotherapy (CT) and somatostatin analogue (SSA) in NET patients in the Auckland Region.

METHODS

There is currently no centralised record of NETs in New Zealand since many are not recorded in the National Cancer Registry. The NETwork! Project aims to address this by compiling a national database of patients with NETs.

Data was collected from the New Zealand Cancer Registry and ADHB pathology as part of a nationwide project on Neuroendocrine cancer. Clinical records of NET patients seen in the Auckland region from 1995-2013 were retrospectively analysed.

Classification of neuroendocrine tumours was defined as per WHO 2010 nomenclature; low grade (Ki-67 0-2%, mitotic count <2 per 10 HPF), intermediate grade (Ki-67 3-20%, mitotic count 2-20 per 10 HPF) and high grade (Ki-67 >20%, mitotic count >20 per 10 HPF).

Neuroendocrine tumours in the analysis included gastroenteropancreatic neuroendocrine tumours, extrapulmonary small cell carcinoma, large cell carcinoma, medullary thyroid carcinoma, merkel cell carcinoma, paraganglioma and phaechromocytoma.

Treatment outcomes included best symptomatic, radiological and biochemical response.
Radiological response was defined as a reduction in size of ≥15% in the sum of 3 representative lesions (to attempt to identify any signals of molecular response).
Symptom response included improvement in performance status or cancer associated symptoms (eg.carcinoid syndrome).
Biochemical response required a reduction of ≥ 30% in two consecutive measurements, at least 1 month apart (eg.Chromogranin A)

RESULTS

169 patients were included in the analysis.
Histological grade was unavailable in 21 patients (12.4%).
Median time of follow-up was 83 weeks.

Histology	Total number of patients (n=169)
GEP-NET	120
High Grade	15
Intermediate Grade	45
Low Grade	42
Not Available	18
Large cell carcinoma	15
Extrapulmonary small cell carcinoma	8
Merkel cell carcinoma	8
Others	18

Table 1: List of NET histology included in the analysis

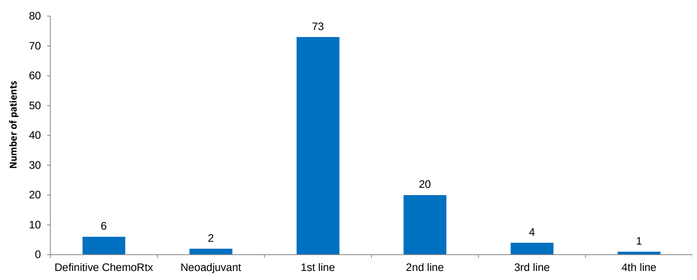

Figure 1: Number of lines of systemic chemotherapy

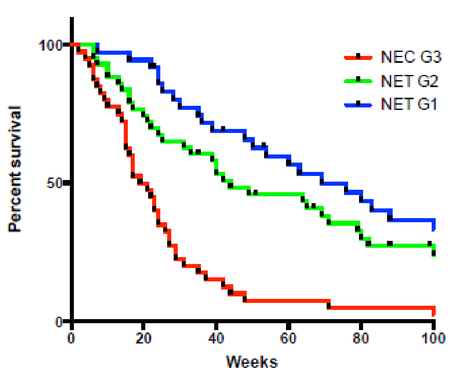

Figure 2: Progression free survival for all patients treated with either systemic chemotherapy or SSA alone in a first line setting, by histological grade.
Log-rank analysis p<0.0001

All Chemotherapy

84 patients had systemic chemotherapy with 106 lines of treatment in total.

Chemotherapy	Definitive ChemoRT	Neoadjuvant	1st line	2nd line	3rd line	4th line	Total
Carboplatin/ Etoposide	2		46	5	1		54
Capecitabine/ Temozolomide			4	4	1		9
Streptozosin/ Doxorubicin		1	3	3		1	8
Cisplatin/ Etoposide	2		2				4
Carboplatin			4				4
FOLFIRI			1	3			4
5FU/ Capecitabine			1	3			4
FOLFOX			2	1			3
Carboplatin/ Paclitaxel			3				3
DTIC/ Vincristine/ Cyclos			3				3
Cisplatin	2						2
Paclitaxel (weekly)					2		2
Gemcitabine			1	1			2
Docetaxel			1				1
Carboplatin/ 5FU			1				1
ECF		1					1
Doxorubicin			1				1
Total	6	2	73	20	4	1	106

Table 2: List of chemotherapy regimens used in NET patients

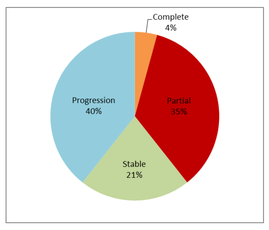

Figure 3: Radiological response was seen in 39% of NET patients treated with all lines of chemotherapy (n=94).
Treatment response was unavailable in twelve cases and was not included in the figure.

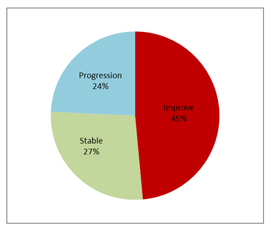

Figure 4: Symptom improvement was reported in 49% of patients treated with all lines of chemotherapy (n=103).
Response was unavailable in three cases and were not included in the above figure

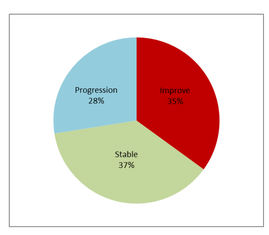

Figure 5: Biochemical response was seen in 35% of patients treated with all lines of chemotherapy (n=40).
Response was unavailable in sixty-six cases and were not included in the above figure

First line Chemotherapy

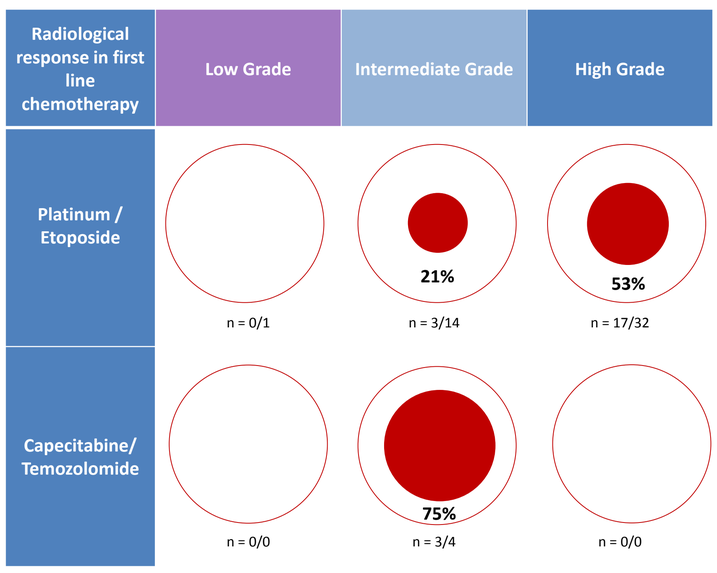

Figure 6: Radiological response (either complete or partial) to platinum/etoposide chemotherapy was increased in high grade NETs compared to intermediate grade NETs (53% vs 21% respectively). There were insufficient cases to make any significant comparisons with capecitabine/temozolomide (n=4) or streptozosin/doxorubicin (n=3) chemotherapy. 5 patients did not have histological grade available and were not included in the above analysis.
When chemotherapy was used in a first line setting (n=63), Complete or partial radiological response was achieved in 43% with median response duration of 16 weeks (5 – 311 weeks). Stable disease was seen in 27% with median response duration of 13 weeks (4 – 42 weeks)

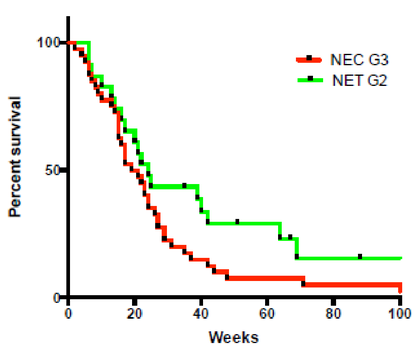

Figure 7: Progression free survival for patients treated with first line chemotherapy, by histological grade.
Log-rank analysis p=0.07

Somatostatin Analogue

93 patients had treatment with SSA either alone or in combination, of which 68 patients were treated with SSA alone.

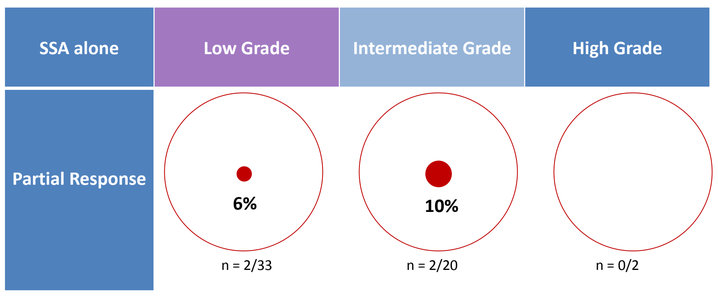

Figure 8: Partial radiological response was higher in intermediate grade NET (10%) compared to low grade NET (6%).
All four patients with partial response by our criteria would have met RECIST 1.1 criteria. Histological grade was unavailable in 13 patients and were not included in the analysis.

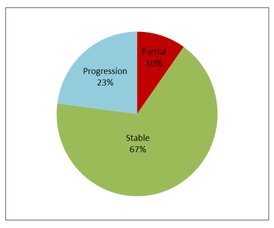

Figure 9: Partial and stable radiological response was seen in 10% and 67% respectively, of patients treated with SSA alone (n=61). Treatment response was not available in 7 patients and were not included in the figure.
Median duration of partial response was 84 weeks (29 – 109 weeks) and median duration of stable response was 68 weeks (5 – 321 weeks).

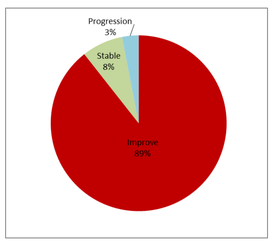

Figure 10: Symptom improvement was reported in 89% of patients treated with SSA alone (n=66).
Response was not available in two cases.

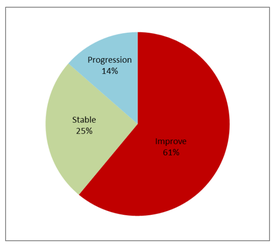

Figure 11: Biochemical response was seen in 61% of patients treated with SSA alone (n=59).
Response was not available in nine cases.

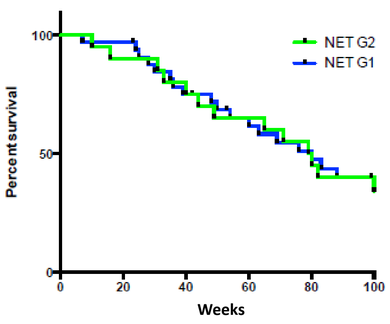

Figure 12: Progression free survival was similar in low or intermediate grades for patients treated with SSA alone.
Log-rank analysis p=0.06

DISCUSSION

Despite NETs being relatively uncommon, the use of a registry enables collection of a large volume of information which can be used to evaluate clinically meaningful outcomes.

The radiological response to first line chemotherapy in our analysis of 43% is consistent with that of literature [1]. There is lower radiological response to first line platinum-etoposide chemotherapy in intermediate grade NETs compared to high grade NETs (21% versus 53% , respectively).

When treated with SSA alone, partial or stable disease was seen in 10% and 67% respectively, comparable to that seen in the PROMID trial [2] (2% partial and 66% stable disease at 6 months).

Limitations of the study include its retrospective analysis with a proportion of patients with unavailable histology or treatment response.

CONCLUSION

1. This study will serve as a pilot for future clinical data extraction from the NETwork Registry as the Registry expands to cover patients throughout New Zealand
2. Combining this data, with similar data from across New Zealand, will create a large and clinically meaningful series that will help guide international best clinical practice

References

(1) Mitry E, Baudin E, Ducreux E et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *British Journal of Cancer* 1999; 81(8): 1351-1358.
(2) Rinke A, Muller H, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomised study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: a report from the PROMID Study Group. *J Clin Oncol* 2009;27(28):4656-65