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Ki-67 Proliferative Index Predicts Response to Chemotherapy and Survival in 252 Patients with High-Grade Gastrointestinal Neuroendocrine Carcinoma (WHO G3)

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Background: Gastrointestinal neuroendocrine carcinoma (GI-NEC) are aggressive tumors and usually metastatic at diagnosis. GI-NEC have a high proliferation rate with a Ki-67 index >20% by definition, but it is often higher (>75%). Treatment of patients with gastrointestinal neuroendocrine carcinoma remains a challenge for the clinician, as published data are very limited on this subgroup of neuroendocrine tumors. We retrospectively reviewed clinical data to identify predictive and prognostic markers for advanced GI-NEC patients.

Methods: Epidemiological, biochemical, histopathological, treatment and survival data were registered for advanced GI-NEC patients treated with chemotherapy during 2000-2009 at 12 Nordic university hospitals.

Results: 252 patients were included. Response rate to 1st-line chemotherapy was 31%, 33% had stable disease, and median survival was 11 months. Ki-67<55% was by ROC analysis the best cut-off value concerning correlation to response rate. Response rate to 1st-line 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 platelets or lactate dehydrogenase (LDH) levels at baseline. Survival and response rates did not differ between the different platinum

chemotherapy schedules (cisplatin-based vs. carboplatin-based) or morphological subtypes. Patients with Ki-67<55% had longer median survival (15 months) than patients with Ki-67≥55% (10 months) ($p<0.001$).

Conclusions: GI-NEC patients with Ki-67<55% had significantly longer survival than patients with higher Ki-67, but were much less responsive to platinum-based chemotherapy. Platinum-based chemotherapy may not be the optimal chemotherapy schedule when Ki-67<55%. Our data indicate that it might not be correct to consider all GI-NEC as one single disease entity (WHO G3) as in the present WHO classification.