Treatment of neuroendocrine tumours of the gastrointestinal tract

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Introduction

Neuroendocrine tumours (NE) of the gastrointestinal tract and pancreas constitute about 2% of all malignant tumours. They include a number of different tumours, derived from cells of the diffuse neuroendocrine cell-system[1]. The largest group of NE tumours are the so called carcinoids, with an incidence of about 2.5/100.000[2], which by tradition have been divided into foregut, midgut and hindgut tumours. Endocrine pancreatic tumours has an incidence of 0.4-0.8/100.000. This old classification is based on the embryonic origin of the different tumours, where the foregut carcinoid primaries has been located in the lung, thymus, gastric mucosa and the midgut carcinoids with primary tumours in the ileum, caecum and proximal colon and the hindgut carcinoids with the primaries in the distal colon and rectum. This old classification is now about to be abandoned, and more tumour-biology-based classification has emerged. The new WHO-classification is now indicating five subtypes[3].

1. Well-differentiated endocrine tumour
2. Well-differentiated endocrine carcinoma
3. Poorly-differentiated endocrine carcinoma
4. Mixed exocrine and endocrine carcinomas
5. Tumour-like lesions

This classification can be used for all types of NE tumours, not only for carcinoids. A classical midgut carcinoid will be called with the new terminology A well-differentiated endocrine carcinomas of the ileum, whereas a benign insulin producing tumour of the pancreas will be A well-differentiated endocrine tumour of the pancreas. The differentiation between different tumours types is based on histomorphology, tumour-size and presence or absence of local invasion and/or metastases. This new classification of NE tumours is a step forward, although the former classification of carcinoid tumours into foregut, midgut and hindgut, remains clinically available and is still used in many clinical studies. It will take some time for the new classification to receive general acceptance.

NE tumours exhibit substantial differences in terms of genotype and phenotype. Foregut carcinoids mainly pulmonary, but also endocrine pancreatic tumours, frequently show losses of 11q, which represent a characteristic genetic alteration in these tumours. Both typical and atypical carcinoids of the lung show loss of heterozygosity at 11q13, harboring the multiple endocrine neoplasia Type 1 (MEN-1) gene. Atypical carcinoids also show loss of heterozygosity at 3p14-p21.3. Recent studies have shown that carcinoid tumours of the lung and the GI tract may develop via different molecular pathways. Inactivation of one of several tumours suppressor genes on chromosome 18 may be important for the biological behaviour of GI tumours. Familiar midgut carcinoids are rare but bronchial carcinoids as well as endocrine pancreatic tumours and gastric carcinoids may be part of a MEN-1 syndrome[4, 5].

Such differences in molecular genetics and tumour biology play a role for the diagnosis and treatment of neuroendocrine gastrointestinal tumours.

Treatment of NE tumours

Surgery

The clinical management of metastatic NE tumours requires a multimodal approach including surgery and other means of cytoreductive treatment, radiotherapy and medical treatment. Surgery remains the treatment of choice and is the only approach that can achieve a complete cure in patients with NE tumours. In cases of metastases, surgery has been used to improve hormone-mediated symptoms, quality of life and survival in certain groups of patients, as well as to reduce tumours bulk and prevent further local and systemic effects. Surgical resection of primary tumours as well as lymph nodes and liver involvement can improve survival. In addition, surgery can also be employed after medical treatment to achieve substantial tumour reduction in an attempt to maxi-

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TABLE IA

Cytotoxic therapy for carcinoid tumours

Drug	Regimen	Number of patients	Overall response (%)	Median duration (months)
Single agents				
Doxorubicin	60 mg/m^2 every 3-4 weeks	81	21	6
5-Fluorouracil	500 mg/m^2/day x 5 every 5 weeks	30	17-26	3
Streptozotocin	500-1500 mg/m^2/day x 5 every 3-5 weeks	14	0-17	2
Dacarbazine	250 mg/m^2/day x 5 every 4-5 weeks	15	13	4.5
Cisplatin	45-90 mg/m^2 every 3-4 weeks	16	6	4.5
Combinations				
Streptozotocin + 5-fluorouracil	500 mg/m^2/day x 5 every 3-6 weeks 400 mg/m^2/day x 5 every 3-6 weeks	175	7-33	3-7
Streptozotocin + doxorubicin	1000 mg/m^2/week x 4 25 mg/m^2/week then every 2 weeks	10	40	5
Streptozotocin + cyclophosphamide	500 mg/m^2/day every 6 weeks 100 mg/m^2 once every 3 weeks	24	39	6.5
Etoposide + cisplatin	130 mg/m^2/day x 3 45 mg/m^2/day on day 2 and 3, repeat cycle every 4 weeks	13	0	-

mize the disease-free interval[6, 7]. Surgery and thermal ablation (radiofrequency treatment) are new promising methods for treatment of liver metastases. Significant clinical improvement and reduction in tumour size has been reported[8, 9].

Liver transplantation has been suggested in selected patients without residual extrahepatic manifestations. However, long-term results are not that encouraging at the moment and the liver transplantation should only be reserved for a very few patients, where other means of therapy cannot control the disease[9].

Enbolization/chemoenbolization

A significant number of patients carry liver metastases at diagnosis, therefore treatment aimed at reducing the tumour bulk in the liver may significantly improve quality of life and survival. Such procedures include embolization of liver metastasis with or without concomitant cytotoxic agents (chemoembolization). Objective symptomatic and hormonal responses are ranging from 65% to 80%, but the method must be repeated to achieve long-lasting responses.

Radiotherapy

External radiotherapy has demonstrated limited value. Today this kind of therapy is mainly reserved for treatment of brain metastases and pain related to bone metastases. Tumour-targeted radioactive treatment using radiolabeled somatostatin analogues have been applied during the last years with some encouraging results. The different compounds have been 111Indium-DTPA-octreotide, 90Y-DOTA-octreotide, 90Y-DOTATOC and MAURITIUS giving about the same results with symptomatic improvement in 40% of the patients, biochemical responses in 24% to 30% and significant tumour reduction in a small number, 5% to 10%. In order to overcome the limitation of administrating doses of radiotherapy to non octreotide avid lesions and the lack of uptake due to tumour heterogeneity in addition to Ytrium 90 several other isotopes such as Lutetium 177 and Rhenium-186 are being considered. 177Lu-DOTA-octreotate shows high tumours uptake with a very good ratio of tumour to kidney uptake and is suggested to be an ideal compound for radionuclear treatment. Radiotherapy with this compound has recently been administered to 80 patients with a variety of progressive NE tumours and 49% showed partial remission[10, 11].

TABLE IB

Cytotoxic Therapy - Endocrine pancreatic tumours

Regimen	No of patients	Over all response rate (%)	Median duration
Streptozotocin	52	42	NA
Streptozotocin +5-FU	106	31-63	14-23 mo
Streptozotocin + Doxorubicin	36	69	18 mo
Streptozotocin + Doxorubicin +5-FU	11	54,5	15 mo

Medical treatment

Medical treatment of NE tumours includes treatment with both chemotherapy and biological agents, such as somatostatin analogues and interferon-alfa.

Chemotherapy (Table Ia, Ib)

Chemotherapy has been considered the gold standard for treatment of most NE tumours, however, it is usually reported for only a limited number of patients and with variable crite-

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TABLE II

Neuroendocrine tumours: somatostatin analogue therapy (summary of several trials)

Response	Standard dose (100-1500 µg/day)	High dose (>3000 µg/day)	*Slow release (20-30 mg/day every 2-4 weeks)*
Symptomatic (%)	64 (146/228)	42 (11/26)	63 (76/119)
Biochemical (%)			
-complete response	11 (6/54)	3 (1/33)	3 (3/119)
-partial response	55 (116/211)	72 (24/83)	64 (76/119)
-stable disease	34 (72/211)	21 (7/33)	18 (21/119)
-progressive disease	11 (23/211)	3 (1/33)	15 (19/119)
Tumour (%)			
-complete response	-	2 (1/53)	-
-partial response	5 (7/131)	11 (6/53)	3 (4/119)
-stable disease	38 (50/131)	47 (25/53)	79 (94/119)
-progressive disease	56 (74/131)	39 (21/51)	18 (21/119)

TABLE III

Therapy with interferon-α in patients with midgut carcinoids

Number of patients	Biochemical response (%)	Subjective response (%)	Tumour value response (%)
29§	PR 53 (13/25)	72 (32/29)	PR 10 (3/29)
	SD 36 (9/25)		SD 86 (25/29)
27§§	PR 39 (9/23)	65	PR 20 (4/20)
16	PR 16 (1/6)		PR 0 (0/16)
	SD 50 (3/6)	80 (4/5)	SD 66 (10/15)
14	PR 44 (4/9)	55	PR 0 (0/16)
13	PR 8 (1/13)		PR 8 (1/13)
	SD 31 (4/13)	50	SD 77 (10/13)

§ Natural leukocyte interferon-α, 6 MU subcutaneously x 8 weeks
§§ High-dose interferon-$\alpha_{,2a}$ 24 MU/m^2 subcutaneously x 8 weeks
PR: Partial response; SD: Stable disease

ria for assessing antitumour responses. Cytotoxic treatment is predominantly used in patients with tumours that show high proliferative capacity and large tumour burden; a proliferation index analyzed by the antibody Ki67 should be above 10% to 15%. Classical midgut carcinoids with low proliferating capacity (Ki67) usually <2%) have not benefited from regular cytotoxic treatment. The most common chemotherapy in endocrine pancreatic tumour is a combination of Streptozotocin plus 5-fluorouracil or doxorubicin. Reported objective response-rates has been between 40% and 70%, whereas in classical midgut carcinoids the same combination has only generated responses of <10% with short duration. For anaplastic tumours and high proliferative capacity (Ki67 above 15%) combination with cisplatinum and etoposide has been particularly useful with a response-rate up to 67% with a tendency to more prolonged survival[12].

Somatostatin analogues (Table II)

The rationale for the clinical use of somatostatin analogues is based on the identification of high-affinity somatostatin receptors in 80% to 90% of NE tumours. Regular octreotide at a subcutaneous daily dose of 200-450 _g is associated with a median 60% symptomatic, 70% biochemical and 8% tumour response. A limited number of patients have been reported with partial tumour regression during treatment with somatostatin analogues, and very few cases have shown complete tumour regression. However, a high number of patients reached disease stabilization. Today slow-release formulations of octreotide Sandostatin LAR® and Somatuline Autogel® have been effective with a monthly dosage of 20-30 mg Sandostatin LAR® or 60-120 mg Somatuline Autogel®. SOM230 is a new somatostatin analogue which has a prolonged half-live, (approximately 24h) and exerts a more potent inhibitory effect than currently available compounds as it binds with much higher affinity to somatostatin receptors 1, 2, 3 and 5. The introduction of SOM230 into clinical practice will address a long-standing question as to whether somatostatin receptor subtypes 1 and 3, which mediate antitumour effects (cell cycle inhibition and induction of apoptosis) will be clinically beneficial in NE tumours[13, 14].

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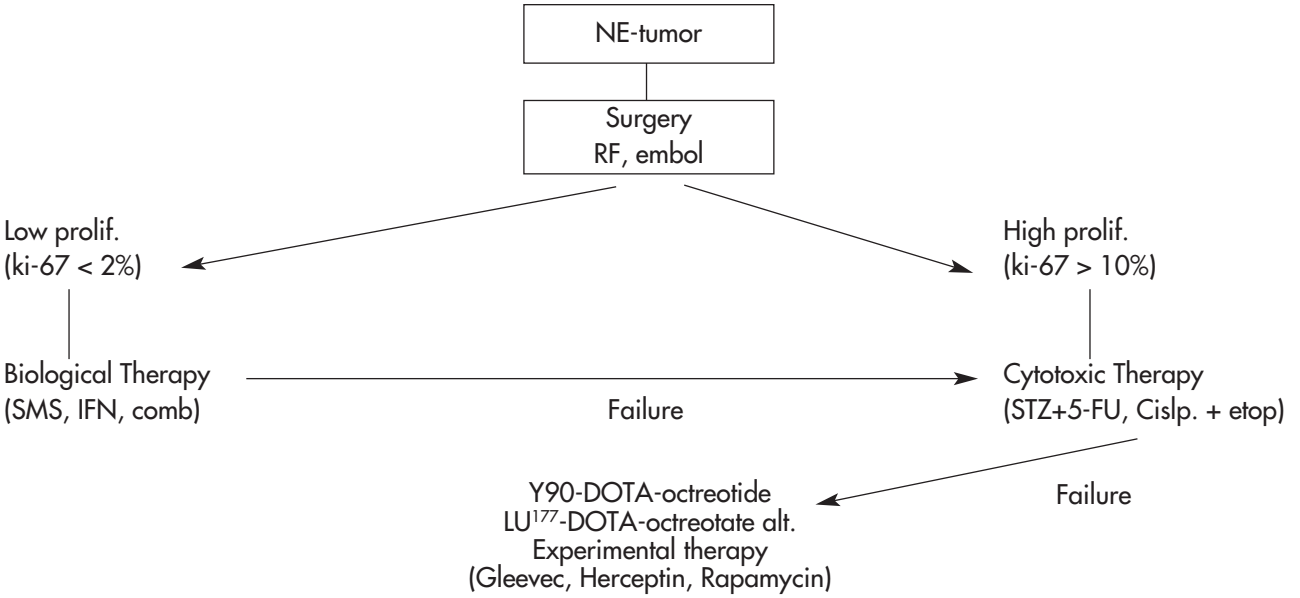

Fig. 1. Algorithm for the therapy of Neuroendocrine Tumours.

Interferons (Table III)

Interferons are compounds known to exert a combination of effects directed to several groups of tumours and are considered as biological response modifiers as they interact with other soluble or cell-associated regulatory factors. The recommended dose of interferon-alfa is 3-9 MU every other day, subcutaneously or slow release formulation pegylated interferon alfa 80-100 μg once a week, subcutaneously. Data derived from several studies of carcinoid tumours have reported a median symptomatic and biochemical response rate of 40% to 70% and biochemical response in 40% to 60% and a significant tumour reduction in 10% to 12% of patients. Disease stabilization is noted in a further 35% of the patients. Flu-like symptoms are almost universal with interferon treatment but are usually short lasting. Chronic fatigue and mild depression may develop in approximately 50% of patients. Autoimmune reactions appear in approximately 15% of patients[15, 16].

Combination therapy with IFNα and somatostatin analogue

Patients for whom mono-therapy with interferon alone or octreotide alone could not control the disease have received the combination. Both hormone levels and clinical symptoms were controlled in 40%-70% of the patients but also tumour growth in one third[16].

The therapy of Neuroendocrine Tumours is summarized in an algorithm (Fig. 1).

New compounds

Inhibition of the intracellular signal transduction from tyrosine kinase receptors may be new targets in the treatment of NE tumours. Many NE tumours express platelet-derived growth factor alfa- and beta-receptor subtypes and ligands and also EGF-receptor. Another interesting new compound is Rapamycin, which may block signal transduction through the m-TOR pathway. Clinical trials with this compound as a single agent or in combination with cytotoxic agents are planned. Over the next five years the precise role of tumour-targeted radioactive treatment with somatostatin analogue-based compounds will be defined. New somatostatin analogues, such as SOM230 and somatostatin receptor subtype-specific analogues will also be developed. The tumour biology for different subtypes of NE tumours will be defined and thus new treatments including tyrosine kinase inhibitors, antiangiogenic compounds as well as combinations of these, will be applied in clinical trials.

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