The potential role of targeted therapies in the management of neuroendocrine tumours

G. Verset[1], I. Borbath[2], T. Delaunoit[3], P. Demetter[4], G. Demolin[5], A. Hendlisz[6] , P. Pattyn[7], S. Pauwels[8], M. Peeters[9], G. Roeyen[10], E. Van Cutsem[11], Ph. Van Hootegem[12], C. Verslype[13], J.L. Van Laethem[1]

(1) Department Gastrointestinal Oncology Unit, Erasme University Hospital, Anderlecht ; (2) Department of Gastroenterology, Cliniques Universitaires Saint-Luc, Brussels ; (3) Department of Gastroenterology and Medical Oncology, Jolimont Hospital, Haine-St-Paul ; (4) Department of Pathology, Erasme University Hospital, Anderlecht ; (5) Department of Gastroenterology and Oncology, C.H.C. St. Joseph, Liège ; (6) Medical Oncology Clinic, Institut Jules Bordet, Brussels ; (7) Department of Gastrointestinal Surgery, University Hospital Gent, Gent ; (8) Department of Nuclear Medicine, Cliniques Universitaires Saint-Luc, Brussels ; (9) Department of Gastroenterology, University Hospital Gent, Gent ; (10) Department of Hepatobiliary, Endocrine and Transplantation Surgery, University Hospital Antwerp, Edegem ; (11) Department of Digestive Oncology, University Hospital Gasthuisberg, Leuven ; (12) Department of Internal Medicine and Gastroenterology, St. Lucas Hospital, Brugge ; (13) Department of Hepatology and Digestive Oncology, University Hospital Gasthuisberg, Leuven.

Abstract

The management of gastro-entero-pancreatic neuroendocrine tumours is evolving thanks to new TNM-classification, diagnostic and staging procedures and new therapeutic options. Targeting new pathways, mostly angiogenesis, development of novel agents is under way and opens new perspectives in controlling the evolution of these tumours and possibly changing their management. In parallel, new functional imaging techniques and biomolecular markers will be developed to provide adequate tools for the assessment of tumor response according to therapeutic intervention on angiogenesis, proliferation and apoptosis.

This paper reviews the potential role of new investigational targeted agents which will likely become the backbone of future therapy of neuroendocrine tumors. (Acta gastroenterol. belg., **2009**, 72, **59-62**).

Key words : neuroendocrine tumours, targeted therapy.

Introduction

The management of neuroendocrine tumors is evolving based on a new classification, new diagnostic and staging techniques and innovative agents. Nevertheless, complete surgical resection remains the only curative treatment of gastro-entero-pancreatic neuroendocrine tumours (GEP NETs), but can only be performed in 20% of the cases. Moreover, debulking surgery may also be considered – even with a non-curative intent – to control debilitating symptoms of hormone overproduction.

Therefore, before considering other strategies, the surgical option should always be revisited even in patients with bilobar liver metastases who can benefit from a two-stage hepatectomy (1).

For patients with advanced GEP-NETs who are not candidate for surgery, local ablation techniques or transarterial chemoembolisation and effective systemic therapy need to be considered. Currently, somatostatin analogs are the treatment of choice in first-line for hormone producing GEP NETs. Although the introduction of these analogues has significantly decreased the morbidity and mortality associated with carcinoid syndrome, tumour regression occurs in < 5% of cases (2).

Cytotoxic agents have limited efficacy, and chemotherapy is only considered as the first-line treatment for patients with poorly-differentiated GEP NETs (3).

Therefore, development of novel therapeutic strategies for GEP NETs is clearly needed and will challenge current bio- and chemotherapy.

The molecular processes that drive the development of NETs are complex, and abnormalities in several cellular signalling pathways have been implicated in NETs tumourogenesis, rendering them potentially susceptible for targeted therapies (4-8). These innovative therapies, aiming to target new pathways involved in GEP-NETs, are reviewed in this paper.

Targeting the VEGF pathway

NETs are highly vascularised and several studies have demonstrated that NETs overexpress vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFR), rendering them potentially susceptible for anti-angiogenic therapies (9,10).

Therefore, several phase II studies have been performed using a variety of VEGF blocking agents or VEFGR tyrosine kinase inhibitors, including bevacizumab, sunitinib, sorafenib, vatalinib and pazopanib. The results of these trials are summarised in table 1.

The efficacy of bevacizumab, a monoclonal antibody against VEGF, was recently demonstrated in a randomised phase II trial in which patients patients received octreotide plus bevacizumab versus octreotide plus pegylated interferon alpha-2b (PegIFN) for 18 weeks. At 18 weeks or at disease progression, patients received bevacizumab plus PegIFN until progression. A higher progression free survival (PFS) rate at 18 weeks in the

Correspondence to : Pr. J.L. Van Laethem, Gastrointestinal Oncology Unit, Department of Gastroenterology, Erasme University Hospital, ULB, Route de Lennik 808, 1070 Brussels. E-mail : JL.Vanlaethem@erasme.ulb.ac.be

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Table 1. — **Results of phase II studies of targeted therapies in NETs**

Agent	Target & mechanism	Type of trial	Response rate	Stable disease
Bevacizumab (11)	VEGF mAb	Randomised Phase II	18%	77%
Sunitinib (12)	VEGFR1-3, PDGFR, c-Kit, RET, FLT3, Tyrosine kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	2% 15%	83% 68%
Sorafenib (13)	VEGFR2-3, PDGFR, FLT3, BRAF, c-Kit, FGFR-1 Tyrosine kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	7% 17%	
Vatalanib	VEGFR1-3, PDGFR, c-Kit Tyrosine kinase inhibitor	Phase II	0%	
Pazopanib	VEGF tyrosine kinase inhibitor	Phase II	In progress	
Temsirolimus (16)	mTOR Protein kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	4,8% 6,7%	
Everolimus (17)	mTOR Protein kinase inhibitor	Phase II Gastro-enteric NET Pancreatic NET	13% 27%	80% 60%
Imatinib (18)	PDGFR, c-Kit Abl inhibitor	Phase II	4%	
Gefitinib (19)	EGFR inhibitor	Phase II	4%	
rH-Endostatin (20)	Endogenous endothelial inhibition	Phase II	0%	
Thalidomide	VEGF & bFGF	Phase II	0%	

bevacizumab arm was obtained (95% vs 68% ; p = 0,02). Moreover, 18% of patients achieved a partial response with bevacizumab and a rapid and sustained decrease in tumour perfusion was observed using functional computerised tomography scan (11).

Sunitinib malate, a small molecule kinase inhibitor with activity against a number of tyrosine kinase receptors including VEGFRs (as well as platelet-derived growth factor receptors (PDGFR), stem-cell factor receptor, glial cell-line-derived neurotrophic factor, and FMS-like tyrosine kinase-3) showed also activity in a non-randomised phase II study performed in patients with metastatic GEP-NETs. Patients were treated with repeated 6-week cycles of oral sunitinib (50 mg/d for 4 weeks, followed by 2 weeks off treatment) until disease progression or unacceptable toxicity. In this trial, the overall objective response rate and the median time to progression were respectively 16.7% and 7.7 months in pancreatic NETs, and 2.4% and 10.2 months in gastro-enteric NET patients. Stable disease (SD) was observed in 83% of carcinoïd patients and 68% of pancreatic NETs. No significant difference from baseline in patient-reported quality of life or fatigue was observed during treatment (12).

On the other hand, sorafenib, a multikinase inhibitor with anti-angiogenic, pro-apoptotic and raf kinase inhibitory activities, was also evaluated in a phase II study in patients with advanced NETs, at the dose of 400 mg orally BID. According to the RECIST criteria, 10% of the patients had a partial response. If they included the patients with minor response, the response rate reached 17% in gastro-enteric NET and 32% in pancreatic NETs. Nevertheless, this treatment is poorly tolerated with 43% of grade 3-4 toxicities (skin (20%), gastro-intestinal (7%) and fatigue (9%) are most common) (13).

Based on these encouraging results, randomised phase III trials assessing the survival impact of bevacizumab and sunitinib are underway.

Targeting mTOR pathway

The mammalian target of rapamycin (mTOR), a highly conserved serine/threonine kinase, plays a central role in the regulation of cell growth in response to environmental factors. Upstream in the growth-promoting pathways that converge on mTOR are critical molecules that are often deregulated in some cancers. Several mutations found in tumours produce inappropriate signals that activate the mTOR switch, driving the growth and proliferation of the tumoral cell. Newly emerging data suggest that mTOR may also play a significant role in the development of NET. It has been shown that IGF-1 activates the PI3-K/Akt/mTOR pathway and promotes tumour growth in human NET cells (14,15).

Phase II clinical trials with mTOR inhibitors (temsirolimus and everolimus) showed interesting results. While a modest clinical benefit was observed with temsirolimus, the results derived from everolimus (RAD001) were more promising (16). Actually, the

recent published trial with everolimus (5 mg/d for the 30 first patients and 10 mg/d for the 30 others) administrated in combination with 30 mg octreotide LAR in 60 patients with advanced NETs, has shown an intent-to-treat response rate of 20% and a median overall PFS of 60 weeks. In the *per protocol* analysis, they observed 27% of partial response and 70% stable disease. Stratified by RAD001 dose, there were 13% PR in the 5 mg cohort and 30% in the 10 mg cohort ; proportionally, there were more pancreatic NETs in the 10 mg regimen. This combination (RAD001 + octreotide) was well tolerated with grade ¾ toxicities < 10%, the most common toxicity being aphtuous ulcerations (17).

Evidence for long-term clinical benefit in patients with advanced NETs awaits the results of two ongoing trials using RAD001, named RADIANT program for RAD001 In Advanced Neuroendocrine Tumour. RADIANT-1 is a multinational open-label, stratified, single-arm phase II study of RAD001 in advanced pancreatic NETs ; RADIANT-2 is a randomised double-blind, placebo-controlled, multicenter phase III study of octreotide and 10 mg/d RAD001 or placebo in advanced carcinoid tumours and RADIANT-3 has the same design in pancreatic NETs.

Targeting PDGF pathway

Platelet-derived growth factor (PDGF) and its receptor (PDGFR) are commonly expressed in NETs. Nevertheless, only an anecdotic clinical efficacy was observed in a phase II study using imatinib (a PDGF inhibitor) at the high dose of 800 mg/d (18).

Targeting EGFR pathway

Although several data suggest a role for the epidermal growth factor receptor (EGFR) in the pathophysiology of NETs, a phase II clinical trial has recently demonstrated no activity using gefitinib – a small molecule (19).

Summary and research agenda

Effective systemic therapy options for advanced GEP-NETs are lacking, and the development of novel agents is clearly needed. Several recent data have demonstrated that a variety of signalling pathways are upregulated in NETs, rendering them potentially susceptible to agents targeting these pathways.

The most promising results were observed with mTOR and VEGF/VEGFR inhibitors, but radiological response rates are still < 20% using RECIST criteria. Stabilisation rate are high with angiogenic and mTOR inhibitors but the interpretation of this should be cautious because of the relatively indolent behaviour of NETs. In this setting, new functional imaging techniques are likely required to evaluate more precisely the activity of these agents and the tumoral response according to the therapeutic intervention, using computed tomography, octreo(PET)scan or dynamic magnetic resonance imaging. Translational research exploring these tools should parallel investigational well-designed trials that evaluate intervention on angiogenesis, proliferation and apoptosis in order to define newer and finer criteria of antitumoral activity. Similarly, the role of EGFR, including Kras gene status, VEGF/R, PDFGR, FGFR, IGFR/Akt/mTOR pathways and their interaction in tumor biology should also be evaluated as predictor of activity of the novel agents tested.

Moreover, combination of these (multi)targeted therapies should be evaluated, relying on a comprehensive evaluation of specific biomarkers.

There is no doubt that this category of new drugs will challenge in the future the existing bio- and chemotherapies, their mechanisms of action being better adapted to the tumor biology of GEP NET. This may be probably also applicable to the adjuvant setting following resection of the primary tumor or metastases.

Meanwhile, their use and place in GEP NET management remains experimental and should be done in investigational setting.

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