Locoregional and radioisotopic targeted treatment of neuroendocrine tumours

A. Hendlisz[1], P. Flamen[2], M. Van den Eynde[1], I. Borbath[3], P. Demetter[4], G. Demolin[5], P. Pattyn[6], S. Pauwels[7], M. Peeters[8], G. Roeyen[9], E. Van Cutsem[10], Ph. Van Hootegem[11], J.L. Van Laethem[12], C. Verslype[13], T. Delaunoit[1-14]

(1) Medical Oncology Clinic, Institut Jules Bordet, Brussels ; (2) Department of Nuclear Medicine, Institut Jules Bordet, Brussels ; (3) Department of Gastroenterology, Cliniques Universitaires Saint-Luc, Brussels ; (4) Department of Pathology, Erasme University Hospital, Anderlecht ; (5) Department of Gastroenterology and Oncology, C.H.C. St. Joseph, Liège ; (6) Department of Gastrointestinal Surgery, University Hospital Gent, Gent ; (7) Department of Nuclear Medicine, Cliniques Universitaires Saint-Luc, Brussels ; (8) Department of Gastroenterology, University Hospital Gent, Gent ; (9) Department of Hepatobiliary, Endocrine and Transplantation Surgery, University Hospital Antwerp, Edegem ; (10) Department of Digestive Oncology, University Hospital Gasthuisberg, Leuven ; (11) Department of Internal Medicine and Gastroenterology, St. Lucas Hospital, Brugge ; (12) Department of Gastroenterology, Gastrointestinal Oncology Unit, Erasme University Hospital, Anderlecht ; (13) Department of Hepatology and Digestive Oncology, University Hospital Gasthuisberg, Leuven ; (14) Department of Gastroenterology and Medical Oncology, Jolimont Hospital, Haine-Saint-Paul.

Abstract

Gastro-entero-pancreatic neuroendocrine tumours (GEP NET) are a heterogeneous group of proliferative disorders whose management dramatically relies on tumour biology. For well-differentiated, low-proliferative index tumours, locoregional treatment and targeted radioisotopic therapies offer an attractive and seemingly efficient alternative to palliative surgical resections. Lack of well-designed, prospective, randomized multicentric studies hinders a balanced evaluation of available locoregional treatment methods : embolization, chemo-embolization, radio-embolization.

According to available datas, all techniques achieve a 50-60% radiological response rate and almost 80% of symptomatic relieve for the patients, while their impact on progression-free and overall survival remains not assessable.

Same conclusions can be drawn for radiolabeled targeted therapies like MetaiodoBenzylGuanidine (MIBG) and Peptide Receptor Radionuclide Therapy (PRRT), which, provided that their target is expressed by tumour cells, can deliver therapeutic doses of radiation to neoplastic tissues.

^{131}I-MIBG has been associated with a 50% symptomatic response rate and mainly haematological toxicities. PRRT with ^{111}In-DiethyleneTriamineentaacetic Acid-Octreotide, [^{90}Y-DOTA^{0}-Tyr^{3}]-Octreotide, or [^{177}Lu-DOTA^{0}-Tyr^{3}]-Octreotate seem to alleviate symptoms in 50% of patients and obtain a radiological response in 30-38%. Renal toxicity, partially preventable, is more frequent than previously thought and result in an annual decrease in glomerular function by 4 to 8% per year.

Forthcoming research in GEP NET should by a majority be designed in randomized, prospective and multicentric fashion. Locoregional disease trials must focus on clinical outcome differences between embolization techniques (embolization, chemoembolization and radioembolization) and surgery.

In disseminated disease, studies should assess radiolabeled targeted therapies efficiency when administered along with and compared to new biological and older chemotherapeutic agents. (Acta gastroenterol. belg., **2009**, 72, **44-48**).

Key words : neuroendocrine tumours, NET, targeted therapy, nuclear medicine, locoregional treatment.

Introduction

Gastro-entero-pancreatic neuroendocrine tumours (GEP NET) belong to a clinically heterogeneous group of neoplasia. Their behaviour, fast growing or, on the contrary, extremely indolent, is predictable by histology and immunohistochemistry (1), more accurately than by other staging systems (TNM, tumour origin ...). More than 2% Ki67-positive cells, angio- and/or perineural invasion, more than two mitoses/10 high power fields (2 mm^2), p53 overexpression and poorly differentiated tumours are associated with a bad prognosis.

Therapeutic strategies have been accordingly developed (2,3) : poorly differentiated tumour expressing a high proliferating index, considered as highly aggressive cancers, should be treated with systemic cisplatin-based chemotherapies. Locoregional treatments have, in that setting, few, if any, indications.

On the opposite side, well differentiated low-expressing Ki67 tumours could initially be considered for loco regional approaches (4,5) with curative or palliative intent. Total or near complete resection of the tumour bulk is suggested as efficient in alleviating symptoms and prolonging life, although such aggressive surgical strategy lacks validation by randomized prospective trials compared to more conservative approaches in palliative setting (6). When surgery is unfeasible or undesirable, alternative loco regional treatments are available : embolization, chemo- or radioembolization for liver only or liver-dominant neuroendocrine metastases (7,8,9,10, 11), targeted MIBG or somatostatin analogs based radiolabeled procedures (12).

The purpose of this review is to analyze available data about regional approaches for liver-localized or -dominant disease and targeted radioisotopic therapies for well differentiated disseminated endocrine tumours, attempting to define their place in modern therapeutic arsenal and to suggest new therapeutic algorithms to be tested in further randomized studies.

Correspondence to : A. Hendlisz, M.D., Digestive Oncology Unit - Medicine Service, Institut Jules Bordet, Université Libre de Bruxelles, Rue Héger-Bordet 1, 1000 Bruxelles, Belgium. E-mail : alain.hendlisz@bordet.be

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A. Locoregional treatment for liver-only or liver-dominant metastatic neuroendocrine tumours

1. *Surgery :* Surgery, assessed only in retrospective series, has become a reasonable option for localized and generalized neuroendocrine tumours. However, this therapeutic option should be carefully weighted for potential benefit versus side effects and complications.

Five years survival rates observed with surgery are comprised between 72% and 83% (6), however available series included only 13 to 61 patients with great heterogeneity in patients population (mixing palliative and curative intent) and surgical procedures (6,9). Postoperative morbidity and mortality seem comparable to usual complications after resection for non-neuroendocrine metastatic tumours at major centres. Mortality rates are reported between 1.2% and 6% and major morbidity rate around 15% (13).

Palliative surgery should not be undertaken in disseminated disease when tumour characteristics are unfavourable (poor differentiation, high proliferate index with more than 10% Ki67-expressing cells), but also when tumour involvement exceeds more than 50% of the liver volume and when less than 90% of tumour volume can be debulked (6,13). Only 10% of patients with liver involvement from neuroendocrine tumours are suitable for surgical resection.

2. *Hepatic Artery Embolization :* Neuroendocrine tumour metastases are richly vascularized, prompting many clinicians to use Hepatic Artery Embolization (HAE) which demonstrated some success in reducing tumour size and hormone output, resulting in symptoms palliation. During this procedure, the hepatic artery is catheterized, and the embolic agent (polyvinyl alcohol particles or gel foam powder) is injected until substantial slowing of the blood flow. In the biggest retrospective series available (161 embolizations for 84 patients), an objective radiological response rate has been reported in 47.8% of cases. Symptomatic improvement occurred in 80% of the patients (8). Major side effects were either hormone-related symptoms (49% of patients experienced post-procedural diarrhea and flushing) or pain (17%). Carcinoid crisis, a rare but severe complication of NET embolization, should be prevented by prophylactic administration of octreotide, given by constant intravenous infusion at a dose of 50 mcg/h for 12 hours prior to and at least 48 hours after surgery (14). Hepatic artery embolizations should be avoided in case of increased risk of biliary bacterial contamination (surgery with biliary sutures, post-sphincterotomy status, bile duct stenting, ...) (15).

3. *Hepatic arterial chemoembolization :* since hepatic metastases derive most of their blood supply from the hepatic artery, regional delivery of chemotherapy offers pharmacokinetic advantages over systemic administration. Hepatic arterial chemoembolization (HACE), combining embolization and intra-arterial delivery of chemotherapy, has also been investigated without adding a convincing advantage over HAE (7,16). No prospective randomized study is available and all publications are based on one single center experience, mixing moreover often several tumour biology's and histology's. Unbiased analysis of the results is therefore impossible. HAE and HACE procedures can be repeated but experience is very limited and results difficult to interpret.

4. *Hepatic Artery Radioembolization* with Yttrium^{90} (^{90}Y) labeled particles is an elegant variation to chemoembolization. Yttrium 90 is a pure b emitter achieving an average range of penetration of 5 mm in tissues with the standard dose of 2 gigabecquerel (GBq) contained in 50 million resin microspheres. It has been used with some success in liver tumoral processes from colorectal cancer (17,18) hepatocellular carcinoma (19), and neuroendocrine tumours (10,11,21).

Pre-therapeutic work-up include a hepatic angiogram with 99m technetium-

labeled macroaggregated albumin (99mTc-MAA) scintigraphy to demonstrate

any aberrant hepatic anatomy, distribution of isotope within the liver, and the percentage of pulmonary shunting. High-percentage pulmonary shunting (> 20%) can cause radiation pneumonitis and preclude those patients from the treatment.

Prediction of response using the 99mTc-MAA-tumour-to-normal uptake ratio is feasible. In colorectal liver metastases, a significant metabolic response can be anticipated with a sensitivity of 89% and a specificity of 65% (20).

Complications are generally minor if precautions are taken to avoid microspheres injection in cystic or gastroduodenal artery, and if patients have at baseline a normal hepatic function. Transient abdominal pain and grade I fatigue are reported. Rare but severe Radiation-Induced Liver Disease (RILD) may occur if treatment is administered to patients with previously altered liver function.

Data suffer from the same poor quality than for either surgical or embolization techniques. A single investigator experience retrospective review of 148 patients yields an impressive response rate of 63,2%, with 22.7% of disease stabilization (21).

The hypothetical advantage of this technique on efficacy and predictability of response over more classic embolization techniques should absolutely be assessed in a prospective randomized study before drawing definite conclusions.

Anecdotically, a single centre prospective study on 33 patients shows seemingly interesting results with a hepatic intra-arterial injection of ^{90}Y-DOTA-Lanreotide (22). This original approach has to be validated in further studies, especially confronted to easier systemic injection of radiolabeled peptides.

Embolization, chemo- and/or radio-embolization have never been compared in a prospective randomized trial to surgical palliative management. Although indirect arguments favour surgery (9), the huge bias of available

publications make valid comparison inconclusive. We should nowadays consider those techniques as equivalent and choose treatment plan according to the patient's wishes and local availability of techniques and expertises. Randomized prospective studies are eagerly awaited in palliative setting to define the respective place of surgery and other locoregional treatment sequentially or in combination.

B. Targeted Nuclear therapies for disseminated disease

1. *Meta-IodoBenzylGuanidine (MIBG)*

Neuroendocrine tumours originate from cells programmed to adopt a specific neuroendocrine phenotype. As so, they show characteristic cytoplasmic secretory granules on electron microscopy and may also express active amine precursor uptake mechanisms and/or specific receptors at the cell membrane. Uptake of meta-iodobenzylguanidine (MIBG), an alkyl-guanidine derivative analogue to noradrenaline, reflects rich catecholamine excretion. ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) scintigraphy is able to detect 50% to 61% of carcinoid tumours and 9% of other NET subtypes (23).

Several reports have shown that ^{131}I-MIBG is effective in some patients with metastatic carcinoids, with symptomatic response rates of 49 to 80%, radiological response rates (WHO criteria) of 48% to 76,5%, overall survival ranking between 17 to 28 months and 5-years survival rates from 22% to 59%. The dose-limiting toxicity is medullar and particularly thrombopenia (12,24). A toxicity–dose model for bone marrow suppression has been developed, permitting, with pretherapy dosimetry, to predict the individual degree of bone marrow toxicity and consequently optimize MIBG therapy (25).

All published studies share the same weakness : no randomization, retrospective analysis, single center experiences, mixed tumour types (metastatic carcinoid tumours, metastatic paragangliomas, metastatic somatostatinoma, intestinal smooth muscle sarcoma, pheochromocytomas, gastrinoma, thyroid medullary cell carcinoma), mixed histological subtypes (well or poorly-differentiated tumours), mixed clinical population (symptomatic/asymptomatic, chemotherapy-naïve or chemo-refractory tumours), inaccuracies in dosimetry methods, in tumoral response evaluation, in toxicity reporting. Results and conclusions should therefore be analyzed cautiously.

Provided that the tumour is visible at ^{131}I-MIBG diagnostic scintigraphy, therapeutic injection of ^{131}I-MIBG is feasible, with few and predictable toxicity and can be repeated several times. Symptomatic response is achieved in more than 50% of cases, whereas objective radiological response is more inconstant and less well reported.

The place of therapeutic injections of ^{131}I-MIBG in neuroendocrine tumours remains to be established, and current areas of development are the use of concomitant radiosensitizing chemotherapy, and combined injections of ^{131}I-MIBG and ^{90}Y-DOTATOC (26).

2. *Peptide receptor radionuclide therapy (PRRT)*

PRRT aims to deliver radiation doses to tumours through the receptor-mediated internalization process and subsequent intracellular retention of the radiopeptide.

PRRT with radiolabeled somatostatin analogues is among the most promising recently developed targeted tools in neuroendocrine tumours (27).

Somatostatin receptors are known to be expressed in a large number of human tumours, including neuroendocrine tumours. Somatostatin-derived radioactive probes, designed to target the SSTR-2-overexpressing neuroendocrine tumours, are primarily based on octreotide, a synthetic and metabolically stable somatostatin analogue linked to a chelator able to bind radioactive metals such as ^{111}In, ^{99}mTc, or ^{68}Ga as diagnostic tools. Adequate chelators should also have good affinity for commercially available radio-therapeutic b-emitters such as ^{90}Y and ^{177}Lu.

The first commercially available agent, ^{111}In-diethylenetriaminepentaacetic acid (DTPA)^0-octreotide has only moderate binding affinity to SSTR-2 and to commercially available b-emitters. It has currently been largely replaced by other compounds like macrocyclic chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), which forms thermodynamically and kinetically stable metal complexes. The most frequently used DOTA-coupled, somatostatin-based radiopeptides are [DOTA^0,Tyr^3]-octreotide (DOTATOC) and [DOTA^0,Tyr^3,Thr^8]-octreotide (DOTATATE).

Research is currently focusing on development of somatostatin analogues and compounds with better and broader receptor subtype affinity profile (28).

Initial studies were performed with the administration of high doses of the radiopeptide [^{111}In-DTPA^0]-octreotide (29,30). Objective responses were observed in 2.5 to 8% of cases with an overall clinical benefit estimated in those highly selected populations at 50 to 62% of the patients. Reported side effects were haematological (with an estimated maximum tolerated dose of 100 GBq), and renal.

A superiority of the radionuclide therapy over no treatment at all is suggested by a french team (30) in a non-randomized study were all 32 included patients were intended to be treated with ^{131}I-MIBG or [^{111}In-DTPA^0]-octreotide. 12 patients received no treatment due to non-medical reasons (remarkably no funding by regulatory authorities or patient's refusal). Advantages in overall and progression-free survival favouring treatment are mentioned in the study conclusions when outcomes of treated and untreated patients are compared, but ethical and methodological pitfalls crippling this trial impair its objective analysis.

[^{90}Y-DOTA^{0},Tyr^{3}]-octreotide (27,31) has been assessed in some prospective and retrospective single-centre non-randomized studies with limited numbers of patients. Overall objective response rates between 8,2 and 33% are reported. Important differences in treatment protocol should be noted. Those results seem superior to [^{111}In-DTPA^{0}]-octreotide, however no direct comparison exist in the literature.

A significant reduction of clinical symptoms was recorded in about 50% of initially symptomatic patients. Toxicity was generally mild and involved a 10-15% grade III-IV haematological toxicity whose occurrence is related to the cumulative doses, and a limited incidence of kidney disease. This latter is misreported and probably underestimated like in most published studies due to lack of sufficient follow up. Dosimetric and dose-escalating studies with [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide, with and without renal protection showed no major acute reactions up to an administered dose of 5.55 GBq per cycle.

The somatostatin analogue [DTPA^{0},Tyr^{3}] octreotate differs from [DTPA^{0},Tyr^{3}]octreotide by replacement of the C-terminal threoninol with threonine. Compared with

[DTPA^{0},Tyr^{3}]octreotide, it shows a 9-fold increase in the affinity for the subtype 2 somatostatin receptor and a 6- to 7-fold increase in affinity with ^{177}Lu isotope.

The uptake of radioactivity was comparable in the patient's kidneys, spleen, and liver but was 3- to 4-fold higher in tumours for the same administered dose (27), improving theoretically the therapeutic balance.

In clinical practice, [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate has been associated with a 30% radiological response rate, a 40 months median time to progression, and a 46 months from first treatment overall survival. Reported toxicity is mild, with 9,5% of grade III-IV haematological toxicity, and 62% grade I reversible alopecia. Severe renal or liver toxicity occurred respectively in 0.4 and 0.6% of patients (32). [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate is certainly one of the main eye-catching novelty in the PRRT field.

Due to their marked radiosensitivity, the kidneys are the critical organs in PRRT. Proximal tubular reabsorption of the radiopeptide and the subsequent retention in the interstitium results in renal irradiation, which can be partially prevented by administration of positively charged absorption-competitor molecules, such as L-lysine and/or L-arginine. Despite kidney protection, a median decline in creatinine clearance of 7.3% per year was reported in patients treated with [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide and of 3.8% per year in patients treated with [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate (27,32).

Cumulative and per-cycle renal absorbed dose, age, hypertension and diabetes are considered as risk factors for renal toxicity after PRRT (33).

Acute haematological toxicity grade 3 or 4 is not uncommon, especially with [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide, and the possibility of a mild, but progressive impoverishment in bone marrow reserves has to be considered in repeated cycles. In addition, myelodysplasia or overt leukaemia may develop in patients receiving high bone marrow doses, especially for patients previously treated with alkylating agents (14).

In conclusion, radio-labeled peptide targeted therapy is a very promising new field in diagnostic and treatment of neuroendocrine tumours. It offers for patients bearing peptide-expressing tumours a simple, efficient treatment with acceptable and predictable toxicity. Research is focusing currently on new and better compounds. A huge effort is meanwhile needed in designing prospective randomized multicenter trials to define the place of PRRT in modern management of endocrine neoplasias beside, in addition or instead of systemic therapies.

Summary and research agenda

The heterogenous field of gastro-entero-pancreatic neuroendocrine Tumours has been recently challenged by several diagnostic and therapeutic improvements.

Locoregional approaches by variations on the theme of embolization for limited spread well differentiated low KI67-expressing NET have been proven feasible at low risk of complication and reasonably efficient. The place of every embolization technique is yet to be determined, but the main controversy relies on relative differences, advantages and indications of palliative surgery versus embolization. This should urgently be assessed in scientifically relevant randomized, prospective multicentric trials.

Radiolabeled targeted therapies (MIBG and Peptide Receptor Radionuclide Therapy) have demonstrated a convincing and relatively safe antitumoral activity, adding moreover the possibility of prediction of treatment outcome.

Here again, their relative place in therapeutic algorithms as competitors or co-helpers of systemic drug therapies should urgently be assessed for patients with generalized NET in prospective, randomized multicentric studies.

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