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RESEARCH ARTICLES

Outcome of treating advanced neuroendocrine tumours with radiolabelled somatostatin analogues

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Abstract
Objectives To evaluate the initial response and outcomes (quality of life and presence of side effects) in patients with advanced neuroendocrine tumours (NET) after treatment with radiolabelled somatostatin analogues: ^{90}Y-DOTA-Tyr3-octreotide (^{90}Y-DOTATOC) and ^{177}Lu-DOTA-Tyr3-octreotate (^{177}Lu-DOTATATE).
Material and methods The study included 5 patients with advanced NET referred to European centres for treatment with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE after lack of response to conventional treatment. The mean age was 45.6 years (29–68 years). Response to therapy was assessed according to: (1) RECIST criteria, as complete response, partial response, stable disease or disease progression, (2) post-treatment survival time and (3) quality of life, using the Karnofsky performance index.
Results All patients survived for >20 months after treatment; mean survival time was 28 months. At the time of writing, three of the patients are alive after 20, 26 and 37 months. Partial response was observed in one patient, stable disease in three and disease progression in the fifth patient. A good-to-excellent post-treatment quality of life was observed in all patients.
Conclusion Therapy with radiolabelled somatostatin analogues showed promising results in patients with advanced NET, with a partial response or disease stabilisation in four of the five patients, who have enjoyed an extended survival period and an improved quality of life.

Keywords Neuroendocrine tumours · Radiolabelled somatostatin analogues · ^{90}Y-DOTATOC · ^{177}Lu-DOTATATE

Introduction

Neuroendocrine tumours (NET) constitute a heterogeneous and rare group of tumours derived from neuroendocrine cells distributed throughout the organism. The National Comprehensive Cancer Network (NCCN) describes six groups of NETs: carcinoid tumours, pancreatic islet cell tumours, pheochromocytomas, anaplastic NETs, non-small-cell lung tumours and multiple endocrine neoplasia syndromes I and II [1]. A multidisciplinary approach to the diagnosis and therapy of NETs is required because of the variability of their anatomic localisation and clinical presentation. Surgery is the treatment of choice. Somatostatin analogues and alpha-interferon are employed to control hormonal secretion, general symptomatology and tumour growth. Chemotherapy is considered essential for metastatic undifferentiated tumours [2].

A promising new therapeutic option for metastatic and inoperable NETs [3] is radiometabolic therapy using so-

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matostatin analogues labelled with radioactive isotopes. The molecular basis of this approach is the internalisation and retention of somatostatin analogues in lysosomes of cells that express receptors for the molecule. This therapy therefore requires the tumours and metastases to express these receptors and be visible on somatostatin receptor scintigraphy (Octreoscan®) [4]. Various radiopharmaceuticals have been tested. A complete or partial response has been reported in 24% of patients treated with ^{90}Y-DOTA-Tyr3-octreotide (^{90}Y-DOTATOC) [5, 6], while treatment with ^{177}Lu-DOTA-Tyr3-octreotate (^{177}Lu-DOTATATE) produced a complete or partial response in 36% and disease stabilisation in 41% of patients [7]. An important clinical improvement was observed in all patients treated with these radiopharmaceuticals. The main adverse effect of this approach is nephrotoxicity, caused by irradiation-induced renal damage due to tubular resorption of the radiopharmaceutical. Renal protection protocols involving the infusion of different amino-acid solutions have been tested and allow the administration of high doses [8, 9].

From 2003 to 2006, our department referred five patients with advanced NET to two reference European centres for metabolic therapy. The objective of this study was to review their initial response to the therapy and the outcomes obtained, including quality of life and presence of complications.

Methods

Patients and inclusion criteria

We reviewed the medical records of five patients diagnosed with advanced NET referred to the Nuclear Medicine Department of one of the referring hospitals after they failed to respond to a conventional treatment protocol in the Oncology Departments of two university hospitals in Granada (Spain). This protocol included surgery of primary tumour (when possible), medical treatment, chemotherapy (QT) and in two cases, radiotherapy (RT). We assessed them for inclusion in clinical trials of ^{90}Y-DOTATOC and/or ^{177}Lu-DOTATATE at the European Oncology Institute of Milan (Italy) or Basel University Hospital (Switzerland). For this purpose, ^{111}In-DTPA-octreotide scintigraphy (Octreoscan) was performed at ≥48 h after the last subcutaneous injection of somatostatin analogues or ≥4 weeks after the last dose of long-term somatostatin analogues. In addition, patients' haematic, hepatic and renal functions were assessed by corresponding biochemical parameters.

Protocols for radiometabolic therapy with radiolabelled somatostatin analogues

Each radiometabolic cycle consisted of the slow intravenous injection of the radiopharmaceutical (diluted in physiological saline solution) for 20 min. Regimens varied, with doses of ^{90}Y-DOTA-Tyr3-octreotide (^{90}Y-DOTATOC) ranging from 45 to 200 mCi in 2–3 cycles with 12–16-week intervals, and doses of ^{177}Lu-DOTA-Tyr3-octreotate (^{177}Lu-DOTATATE) ranging from 80 to 200 mCi in 2–3 cycles with 12–16 week intervals. Two patients received both ^{90}Y-DOTA-Tyr3-octreotide (^{90}Y-DOTATOC) and ^{177}Lu-DOTA-Tyr3-octreotate (^{177}Lu-DOTATATE) in different cycles.

Before, during and after injection of the radiopharmaceutical, all patients were continuously infused with amino acids positively charged with different combinations of L-lysine and/or L-arginine. They also received antiemetic and gastric protection treatment. All patients underwent a post-treatment scan at 48 h after injection to compare uptake of the dose in metastases compared with the pretreatment ^{111}In-DTPA-octreotide scan results. This scan served for comparison with scans of the radiopharmaceutical uptake in subsequent treatment cycles.

Follow-up and toxicity

Response to therapy was assessed by studying medical records of the referring oncology department, pre- and post-therapy conventional imaging studies (CT, MRI) and the records of the Nuclear Medicine Department. Patient follow-up ranged from 20 to 37 months. RECIST criteria were used to classify the response to therapy as complete response (CR), partial response (PR), stable disease (SD) or disease progression (DP). Data were also gathered from medical records on post-treatment survival time (months), Karnofsky index-measured quality of life, presence of acute toxicity (vomiting, nausea or haematological disorders) and signs of chronic renal or hepatic toxicity.

Results

The study included 5 patients with NET of different origin at an advanced stage at the time of diagnosis, 4 males and 1 female, with a mean age of 45.6 years (29–68 years) (Table 1). Three patients (nos. 3, 4 and 5) presented with disease progression. The localisation of metastases varied but was predominantly in bone or liver. All had received the conventional treatment protocol (surgery, medical treatment, QT) and some had undergone additional treatments (palliative RT, ^{131}I-MIBG). All five patients were assessed as suitable candidates for treatment with radiolabelled somatostatin analogues.

All patients survived for >20 months, with a mean post-treatment survival time to date of 28 months. At the time of writing, three patients are alive after 20, 26 and 37 months. Comparison of pre- and post-therapy conventional imaging studies showed a partial response in 1 patient, stable disease in 3 and disease progression in 1 patient. Four patients

Table 1 Clinical data (sex, age, primary tumour, extension), radiometabolic therapy characteristics and assessment of the response of patients with NET

Patient no.; sex	Age (years)	Primary tumour	Extension: metastasis	Radiopharmaceutical: protocol and dose	RECIST	Survival (months)	Karnofsky
1, male	64	Well differentiated neuroendocrine carcinoma (unknown primary)	Liver, bone (scapula, spine)	^{90}Y-DOTATOC (2×185 mCi)	Disease stabilisation	37	80%
2, male	29	Poorly differentiated neuroendocrine carcinoma (unknown primary)	Liver	^{90}Y-DOTATOC (1×45 mCi and 1×55 mCi)	Disease stabilisation	28 (Exitus)	90%
			Bone (tegmentum, spine, ribs and pelvis)	^{177}Lu-DOTATATE (1×100 mCi, 1×80 mCi and 1×94 mCi)			
3, male	37	Bronchial well differentiated neuroendocrine carcinoma	Mediastinum, liver, testicle, bone, cutaneous	^{90}Y-DOTATOC (2×200 mCi), ^{177}Lu-DOTATATE (1×200 mCi)	Disease stabilisation	20	80%
4, male	68	Small intestine well differentiated neuroendocrine carcinoma	Peritoneal, liver, mediastinum	^{90}Y-DOTATOC (1×175 mCi)	Partial regression of the disease	26	70%
5, female	30	Bronchial well differentiated neuroendocrine carcinoma	Lumbar spine, hip, ovaries	^{90}Y-DOTATOC (2×160 mCi)	Disease progression	28 (Exitus)	60%

reported a good-to-excellent quality of life (Karnofsky index score 70–90%).

Patient 1

This patient was a 64-year-old male with smoking history and diagnosis of metastasis (in liver and left scapulae) of well differentiated neuroendocrine carcinoma with unknown primary site. He underwent chemotherapy (carboplatin, etoposide and 5-fluorouracil) but there was no reduction in tumour size or 5-hydroxyindoleacetic acid. After ^{111}In-pentetreotide scintigraphy (Octreoscan®) showed a positive result, treatment with ^{90}Y-DOTATOC was started (2 cycles of 185 mCi with a 3-month interval) (Fig. 1). There was a good tolerance and no adverse effects were observed. The treatment produced a stabilisation of tumour mass and decrease in 5-hydroxyindoleacetic acid. After treatment, the patient required fewer drugs and a lower analgesia dose, and his Karnofsky score was 80%. This situation remains unchanged at 37 months after treatment.

Patient 2

The second patient was a 29 year-old male with no history of interest, diagnosed with multiple hepatic and bone metastases (tegmentum, vertebral column, ribs and pelvis) and pathologic diagnosis of a poorly differentiated neuroendocrine carcinoma. ^{111}In-pentetreotide scintigraphy showed uptake at the above sites, but the primary tumour was not localised. Treatment with cisplatin and etoposide was started, but there was no improvement in lesions and his tolerance was poor. Next, ^{131}I-MIBG was administered (2 cycles of 200 mCi each), and lumbar spine lesions were treated with RT, with no improvements observed. Consequently, he underwent therapy with ^{90}Y-DOTATOC (two cycles [45 and 55 mCi] with a one-month interval and showed good tolerance. Due to the massive bone and liver involvement and the previous myelotoxic and nephrotoxic therapies he was switched to ^{177}Lu-DOTATATE. He was administered with two cycles of ^{177}Lu-DOTATATE (100 and 80 mCi), achieving disease stabilisation and quality of life improvement for 5 months until the progression of hepatic lesions. Then, the patient received a new cycle of ^{177}Lu-DOTATATE (94 mCi), and the lesions were stabilised for 1 year. The patient remained working actively and maintained a good quality of life (90% Karnofsky score). After further progression of hepatic lesions, the patient died 28 months after the first DOTATOC dose.

Patient 3

This patient was a 37-year-old male with diagnosis of bronchial well differentiated neuroendocrine carcinoma with hepatic metastases and subcarinal adenopathies. Chemotherapy was started (tegafur, alpha-interferon, carboplatin and

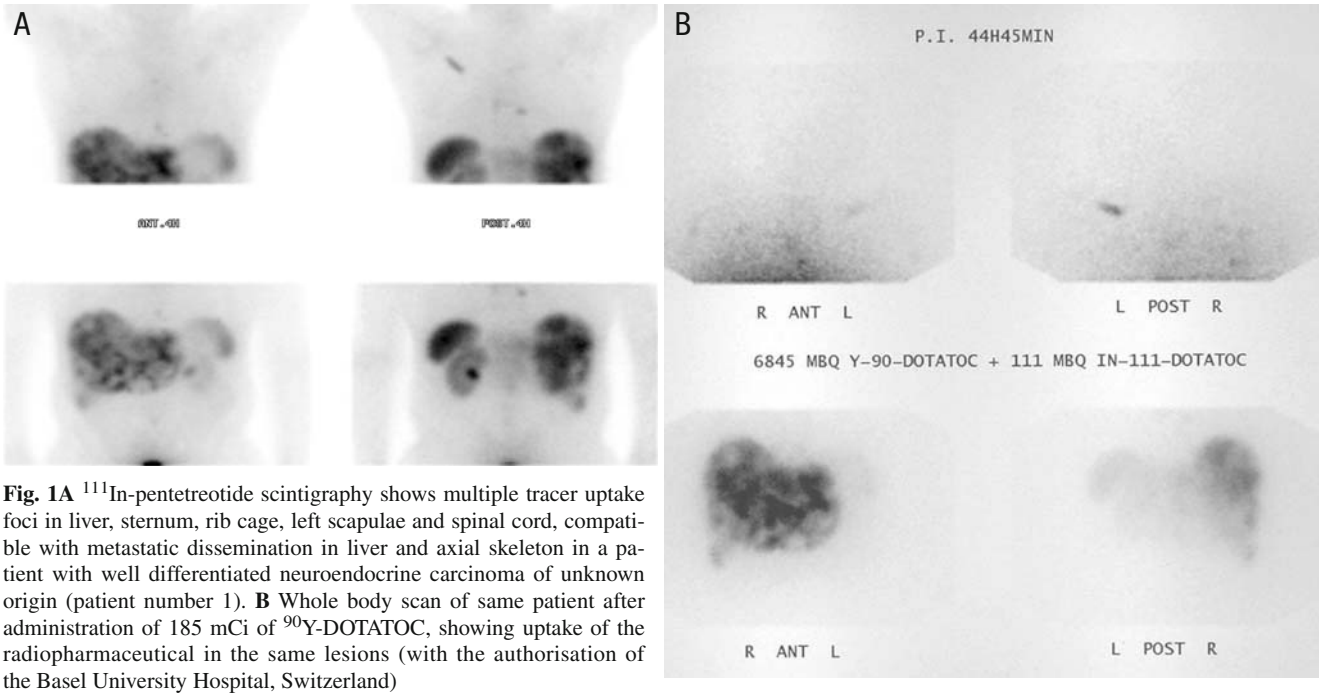

Fig. 1A ^{111}In-pentetreotide scintigraphy shows multiple tracer uptake foci in liver, sternum, rib cage, left scapulae and spinal cord, compatible with metastatic dissemination in liver and axial skeleton in a patient with well differentiated neuroendocrine carcinoma of unknown origin (patient number 1). **B** Whole body scan of same patient after administration of 185 mCi of ^{90}Y-DOTATOC, showing uptake of the radiopharmaceutical in the same lesions (with the authorisation of the Basel University Hospital, Switzerland)

etoposide) but no response was observed in lesions, and new metastases emerged in testes, bone and skin. He was treated with 2 cycles of ^{90}Y-DOTATOC (200 mCi each cycle with 3-month interval) and, one month later, with a cycle of ^{177}Lu-DOTATOC (200 mCi). He showed good tolerance, with no adverse effects, achieving disease stabilisation and good quality of life (80% Karnofsky index). This situation remains unchanged 20 months after treatment onset.

Patient 4

This patient was a 68-year-old male with a history of laryngeal carcinoma and prostate adenocarcinoma. During a study of intestinal and peritoneal lesions, a well differentiated neuroendocrine carcinoma (3.5×2 cm diameter) was detected in peritoneum and multiple well differentiated neuroendocrine carcinomas in small intestine. The peritoneal intestinal tumours were resected, and chemotherapy with carboplatin and streptozotocin was then started. The disease progressed, and new hepatic and mediastinal metastases emerged. He was treated with a 175-mCi dose of ^{90}Y-DOTATOC, showing good tolerance and no adverse effects. The treatment achieved stabilisation of the size and number of lesions, with a post-treatment Karnofsky score of 70%. This situation remains unchanged 26 months after treatment onset.

Patient 5

This patient was a 30-year-old female with a diagnosis of a bronchial well differentiated neuroendocrine carcinoma that required surgical resection. Three months after surgery, she was diagnosed with metastases in lumbar spine and left hip and underwent palliative RT in lumbar spine and chemotherapy (carboplatin, alpha-interferon and etoposide). No clinical response was observed and new metastases emerged in right ovary, which was resected. Consequently, ^{90}Y-DOTATOC was administered, 2 cycles of 160 mCi with a 3-month interval, with no adverse effects. The patient refused to complete a third cycle of treatment, citing discomfort caused by the journey and low emotional state. The bone lesions and general state stabilised (a post-treatment Karnofsky index score of 60%). Several weeks later there was a progression of the disease with the emergence of a metastasis in left ovary, which was surgically resected. The patient died in the postoperative period.

Discussion

A small but relatively homogeneous group of patients with NET was studied. Previous reports on the results of radiometabolic therapy with radiolabelled somatostatin analogues have been based on heterogeneous groups of patients with NETs of varied origin, degree of malignancy and stage [6–8, 17-18]. Our reported patients were diagnoses at advanced stages of their disease and none of them had shown a response to standard treatments. Various therapeutic regimens (total dose, number of doses, inter-cycle interval) have been reported [6–11]. In these patients, ^{90}Y-DOTA-Tyr3-octreotide was administered in 2–3 consecutive cycles of ^{90}Y-DOTA-Tyr3-octreotide with an interval of 3–4

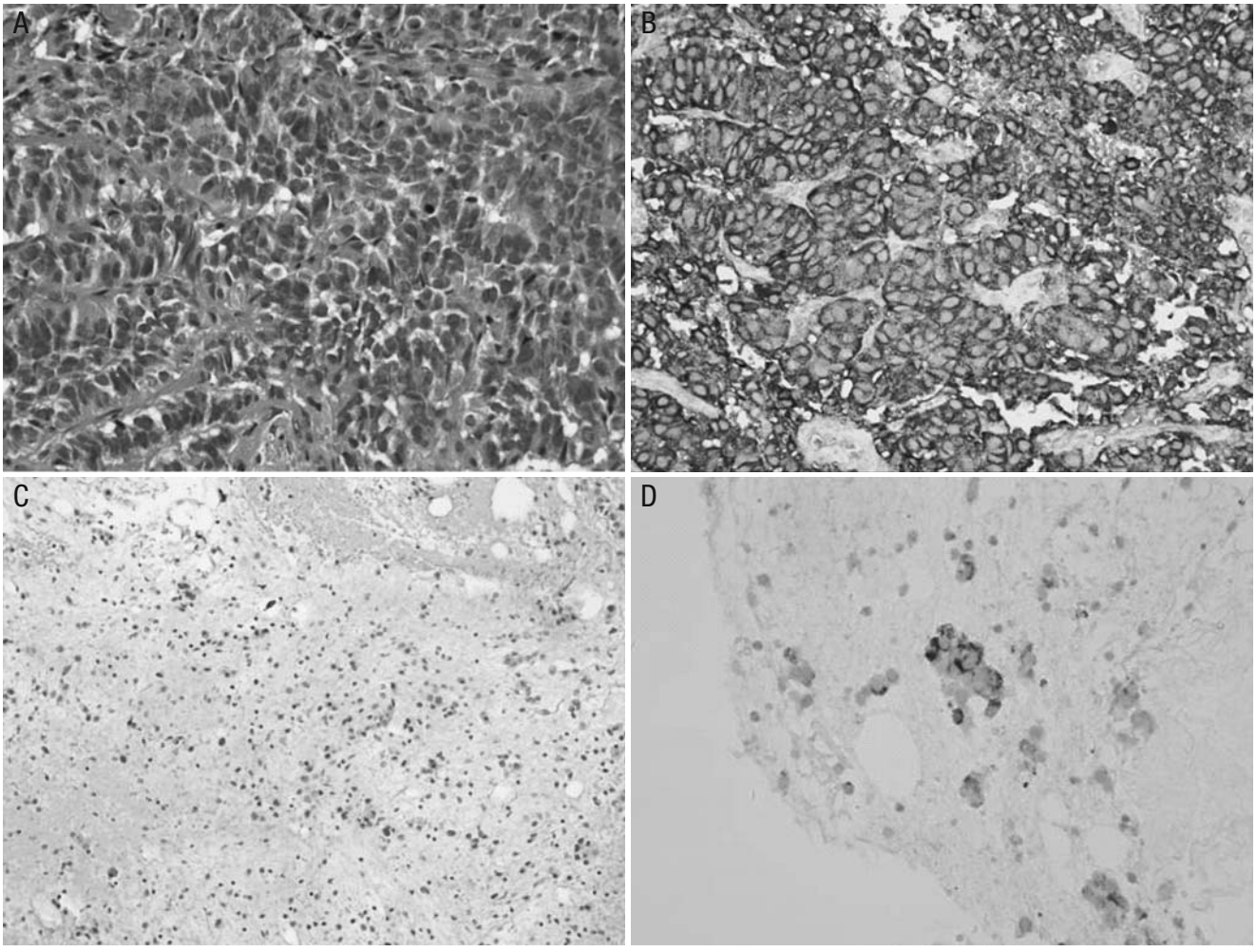

Fig. 2 Images of haematoxylin-eosin staining before **(A)** and after **(C)** radiometabolic therapy with somatostatin analogues and of chromogranin staining before **(B)** and after **(D)** radiometabolic therapy on biopsy of lumbar spine metastasis (patient number 2) showing a reduction in cell and nucleus size (haematoxylin-eosin staining) and a large decrease in chromogranin expression, indicating increased cell differentiation

months. Two patients underwent combined therapy with ^{177}Lu-DOTA-Tyr3-octreotate (^{177}Lu-DOTATATE).

No published survival data could be found for patients in these advanced stages of NET. At the time of writing, the mean post-treatment survival time of our patients is 28 months (minimum 20 months, with three patients surviving after 20, 26 and 37 months). These can be considered highly promising results, since conventional approaches had failed in all cases, and at the time of radiolabelled therapy progressive disease was evident in three out of five patients (patients 3, 4 and 5). They compare favourably with other reports of a mean survival time of 18 months [9]. Valkema et al. published survival periods around 37 months after radionuclide therapy [10]. One of the non-survivors had numerous skeletal metastases in vertebral column at diagnosis, limiting the maximum dose and the other had refused to complete the therapy.

The quality of life of patients after therapy was very good, with a mean Karnofsky score of 75%. Four patients returned to their usual work activity. The worst score was recorded by the patient who refused to complete the therapy. All other patients experienced a significant increase in appetite and weight, with disappearance of carcinoid syndrome. Importantly, the therapy led to a decrease in the dose and number of analgesic drugs used. Our findings are in agreement with previous reports of a very significant improvement in the quality of life of patients after this treatment [6–11]. Only one patient showed a transient decrease in red blood cell and platelet counts with spontaneous recovery. There were no reports of high-grade haematologic toxicity or any signs of renal involvement, explained by pretreatment of the patients with amino-acid infusions. Various researchers have underlined the importance of this preparation, proposing different amino-acid mixtures and protocols that all recommend the longest possible infusion time [4, 11–13]. Alternatives to amino-acid infusions for renal protection are currently under study [14–16].

Numerous studies have reported the antitumour effect of this therapy, as well as the improvements obtained in quality of life and survival [11, 12, 19–21]. In one of our

patients, comparison of pre- and post-treatment CT scans verified a reduction in the size of hepatic lesions. Lesions remained stable in a further three patients: in one of these, comparison between histopathology studies of the biopsies of bone metastases taken before and 3 months after treatment showed a major improvement, with a decrease in nuclear size and cell chromogranin expression (Fig. 2). The patient with disease progression had refused to complete the treatment, citing discomfort caused by the journey and low emotional state.

Four patients with advanced NET responded positively to the treatment, confirming previous reports. Although limited by its small sample size, this reports confirms that this approach potentially offers patients with very advanced stage NET a longer life of good quality and supports the suggestion of starting the therapy in earlier phases of disease. Literature data confirm a high rate of objective response and a consistently longer survival in this patient status [9, 20–22].

Future research lines include the sequenced use of two radiopharmaceuticals in the same course of treatment and the previous administration of radiosensitisers and drugs that increase expression of somatostatin receptors in NETs [21, 23].

Conflict of interest The authors declare no conflict of interest.

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