Indium-111-Pentetreotide Scintigraphy in Children with Neuroblast-Derived Tumors

Luc Manil, Véronique Edeline, Jean Lumbroso, Hélène Lequen and Jean-Michel Zucker
Departments of Nuclear Medicine and Pediatrics, Institut Curie, Paris; and Department of Nuclear Medicine, Institut Gustave Roussy, Villejuif, France

The somatostatin analog ^{111}In-pentetreotide was evaluated in 11 children with sympathetic embryonic cell-derived tumors. **Methods:** Six neuroblastomas, four ganglioneuroblastomas and one ganglioneuroma (benign) were imaged 4 and 24 hr after injection of ^{111}In-pentetreotide (5 MBq/kg) and 24 hr after administration of ^{123}I-metaiodobenzylguanidine (MIBG) (3.7 MBq/kg). **Results:** Primary tumor was detected with both tracers in four of the five patients studied before surgery (one Stage III neuroblastoma, one Stage IV neuroblastoma, one Stage IVs neuroblastoma, one ganglioneuroblastoma), but the ganglioneuroma was not localized. Detection of bone marrow metastases was clearly better with ^{111}In-pentetreotide in two patients, similar or slightly better with MIBG in six and (true) negative with both procedures in three. The positivity rate of ^{111}In-pentetreotide for imaging of metastases was higher in undifferentiated malignant tumors (six neuroblastomas: two very positive, three positive, one true-negative) than in histologically well-differentiated tumors (four ganglioneuroblastomas: three weakly positive, one true-negative). All patients with positive ^{111}In-pentetreotide imaging results had elevated urinary catecholamine levels, and the two most ^{111}In-pentetreotide-positive metastases were found in neuroblastomas from children with an aneuploid primary tumor. The ^{111}In-pentetreotide and MIBG results were only partly correlated with bone marrow status, as assessed by immunocytological and histological studies at the time of scanning. **Conclusion:** Abnormalities detected in ^{111}In-pentetreotide uptake were slightly different from those seen with MIBG, but ^{111}In-pentetreotide is unlikely to replace MIBG as a first-line routine method in neuroblast-derived tumors. However, some MIBG-negative tumor sites were detected by ^{111}In-pentetreotide in patients with neuroblastomas. Thus, ^{111}In-pentetreotide could provide novel information on the biology and prognosis of tumors whose clinical significance remains to be defined.

Key Words: neuroblastoma; ganglioneuroblastoma; indium-111-pentetreotide; iodine-131-MIBG; pediatrics

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Since the first studies demonstrating the feasibility of scintigraphic detection of neuroendocrine tumors with somatostatin analogs such as octreotide, the clinical feasibility of the method has been widely confirmed and extended to a large number of malignancies (*1*). The most significant results with octreotide labeled with ^{123}I (*2*) and subsequently with ^{111}In (*3*) have been obtained in gastroenteropancreatic tumors (*4*), including carcinoids (*5,6*), pituitary tumors (*7*), small-cell lung carcinoma (*8*), breast carcinoma (*9*) and lymphoma (*10*). The use of ^{111}In-pentetreotide instead of ^{123}I-Tyr-3-octreotide has considerably improved tracer availability and image quality (better contrast and lower biliary and intestinal activity but higher renal uptake).

The presence of somatostatin receptors on neuroblastoma cells has been clearly demonstrated (*11–13*). The clinical imaging data with somatostatin published to date concern nine children studied in Rotterdam (*1*), two in Bonn (*14*) and 11 studied by Dörr et al. (*15*). The two cases from Bonn gave discrepant results: positive with metaiodobenzylguanidine (MIBG) and negative with pentetreotide in one, with opposite results in the other. Positive results were obtained in eight of the nine children studied in Rotterdam. According to Kvols [personal communication in Krenning et al. (*1*)], patients with tumors expressing somatostatin receptors might have a longer survival, as also suggested by Dörr et al. (*15*). In the same report, Dörr et al. also concluded that the tracers are complementary because they label distinct tumor subpopulations. Most of these results and some isolated records were recently summarized by Hoefnagel (*16*).

The aim of the present study was to evaluate the respective effects of ^{111}In-pentetreotide and [^{123}I]MIBG in 11 children with neuroblast-derived tumors. Our study focused on children with workup discrepancies or an unexpected course of the disease or with negative or doubtful MIBG scan results. In particular, we investigated a possible correlation between positivity of ^{111}In-pentetreotide imaging and clinical course of the disease, histological differentiation and other paraclinical parameters over a period of approximately 2 yr.

MATERIALS AND METHODS

Patients

Between September 1992 and September 1993, 11 children (5 boys, 6 girls; aged 5 mo–10.6 yr; mean age 54 ± 35 mo) were included in the study. Informed consent was obtained from the parents of all children. Six children had an neuroblastoma (one Stage III, four Stage IV, one Stage IVs); four had a ganglioneuroblastoma (histologically more differentiated than neuroblastoma); and one had a ganglioneuroma (benign mature form). The primary tumor was located in the adrenal area in eight patients, in the abdomen (unspecified) in one and in the mediastinum in two.

Five newly diagnosed children had not undergone operation: Two were untreated (Patients 3 and 7), and three had received induction chemotherapy (Patients 1, 10 and 11). One other patient was included in the study shortly after removal of the primary tumor (Patient 4), and five presented with questionable signs of progression long after the initial treatment: residual MIBG-positive spots with no obvious sign of clinical progression (Patients 5, 6, 8 and 9) or persistent ultrasound and x-ray tumor images but without any MIBG uptake (Patient 2). Among patients who underwent operation, four did not receive any treatment at the time of scanning (Patients 2, 4, 8 and 9), and two were treated with chemotherapy (Patients 5 and 6).

The clinical characteristics of the patients are summarized in Table 1, together with results. Bone and bone marrow status was determined at the time of scanning by cytological, immunocytological (anti-GD2; NSE; CD56) and histological studies (four bone biopsies in bilateral anterior and posterior iliac crests). Bone or

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For correspondence or reprints contact: Luc Manil, MD, Nuclear Medicine, 6 Avenue des Tilleuls, F-9440 Bures-sur-Yvette, France.

TABLE 1
Patient's Clinical Data and Results

Patient no.	Sex	Age at diagn.	Tumor/ Stage at diagn.	Location of primary tumor	BM	Ploidy	Catechol. (urine)	*Nmyc* gene
1	F	3.8 yr	NBIV	Mediastinum	+	Diploid	+	Not amplified
2	F	3.6 yr	GGNB IIIb	Left adrenal gl.	−	NE	−	Not amplified
3	M	3 mo	NBIVs	Right adrenal gl.	+	Aneuploid	+	Not amplified
4	F	3 mo	NBIV	Right adrenal gl.	+	ND	+	Not amplified
5	M	4.10 yr	NBIV	Right adrenal gl.	−	Aneuploid	+	Not amplified
6	M	1.5 yr	GGNBIV VIp	Left adrenal gl.	+	ND	−	Not amplified
7	F	5.5 yr	GGNM	Right abdomen	−	Diploid	−	Not amplified
8	F	1.7 yr	NBIV	Left pararenal	+	Diploid	+	Not amplified
9	F	2.1 yr	GGNBIV	Mediastinum	−	ND	+	ND
10	M	2.3 yr	GGNBIV	Left prerenal	+	ND	+	Not amplified
11	M	3.7 yr	NB III	Right adrenal gl.	−	ND	+	Amplified

Patient no.	Age at scint.	MIBG results	SMS results	Follow-up: From diagn. (July 1995)	Follow-up: From SMS (July 1995)	Clinical status (July 1995)	Comparison: Primary tumors	Comparison: Metastases
1	3.8 yr	T++, M++	T++, M+	3 yr	2.10 yr	PD	Sm = MI	Sm < MI
2	6.8 yr	T++, M°−	T++, M°−	5.7 yr	2.5 yr	CR		Sm° = MI°
3	6 mo	T+, M±	T+, M++	2.7 yr	2.5 yr	CR	Sm = MI	Sm ≫ MI
4	5 mo	T+, M++	T+, M+	2.6 yr	2.4 yr	CR		Sm < MI
5	6.2 yr	T+, M+	T+, M++	3.8 yr	2.4 yr	NP		Sm > MI
6	5.5 yr	T+, M++	T+, M±	3 yr	2.2 yr	NP		Sm < MI
7	5.6 yr	T±, M°−	T±, M°−	2.2 yr	2.1 yr	CR	Sm± = MI±	Sm° = MI°
8	4.11 yr	T±, M++	T±, M+	5.2 yr	1.10 yr	NP		Sm < MI
9	10.6 yr	T±, M++	T±, M±	10.3 yr	1.9 yr	NP		Sm < MI
10	2.3 yr	T++, M++	T++, M±	2.1 yr	2.1 yr	CR	Sm = MI	Sm < MI
11	3.7 yr	T++, M°−	T++, M°−	2.6 yr	3 mo	Deceased	Sm = MI	Sm° = MI°
							0 5 0	2 3 6

diagn. = diagnosis; BM = bone marrow status ([immuno]cytology, histology); Catechol. = catecholamines; scint. = scintigraphy; T = primary tumor; M = metastases; PD = progressive disease; Sm = somatostatin (SMS) scintigraphy; MI = MIBG scintigraphy; gl. = gland; NE = nonevaluable; CR = complete remission; ND = not done; NP = nonprogressive disease; +(++, ±) = moderately (very, doubtful or partly) positive scintigraphic results; −(°−) = false negative (true-negative) scintigraphic results.

bone marrow status was considered positive when tumor involvement was demonstrated by at least one method in at least one site.

Radiopharmaceuticals

Indium-111-pentetreotide labeling was performed in our department, according to the manufacturer's instructions, by mixing 10 μg pentetreotide with 110 MBq (^{111}In)$InCl_3$.

Image Acquisition and Processing

Iodine-123-MIBG and ^{111}In-pentetreotide scintigraphy was performed within 9 days of each other, except in two patients with clinically stable disease (interval 21 and 23 days). Patients received 3.7 MBq/kg [^{123}I]MIBG intravenously (imaging at 24 hr) and 5 MBq/kg of ^{111}In-pentetreotide (imaging at 4 and 24 hr).

Scintigraphic images (whole-body and spot images of the head [lateral views]) were acquired using a large field-of-view rectangular gamma camera fitted with a high-definition low-energy (^{123}I) or medium-energy (^{111}In) collimator.

RESULTS

Somatostatin Image Quality: Comparison of 4- and 24-hour Acquisitions

Images obtained at 24 hr were slightly better than those acquired 4 hr after injection. Tumor contrast was higher, although no additional tumor sites were detected at 24 hr. The initial joint activity disappeared at 24 hr; however, bowel activity appeared at 24 hr and was troublesome in a few patients. Kidney and spleen uptake was prominent at both times, making tumor detection difficult in these areas. Liver activity was lower and not sufficiently intense to preclude detection of liver metastases (Patient 3).

Primary Tumor

Image definition was generally better with MIBG, mainly for physical reasons (gamma spectrum of ^{123}I). Among the five patients undergoing exploration before primary tumor removal, four had comparable positive results whichever tracer was used (Patients 1, 2, 10 and 11). In the last patient (Patient 7), the only child in our series with a mature ganglioneuroma, both studies were inconclusive: Tumor area appeared as a low-contrast shadow, hardly distinguishable from the gut and abdominal background.

Metastases

Comparison with MIBG. Detection of metastases (essentially in bone and bone marrow) was clearly better with ^{111}In-pentetreotide than with MIBG in two patients (Patients 3 and 5), similar or slightly better with MIBG in six (Patients 1, 4, 6 and 8–10) and negative with both procedures in the last three children (Patients 2, 7 and 11).

In Patient 3, with a Stage IVs neuroblastoma (Pepper's syndrome), scan results were strongly positive with ^{111}In-pentetreotide in both the primary tumor and the liver and bone metastases, whereas MIBG was taken up only by the liver (blurred) and the primary tumor, without conclusive evidence of uptake in the bone marrow (Fig. 1). Magnetic resonance imaging of the lower limbs confirmed the ^{111}In-pentetreotide images (focal hypersignal in weighted T2 sequences, corre-

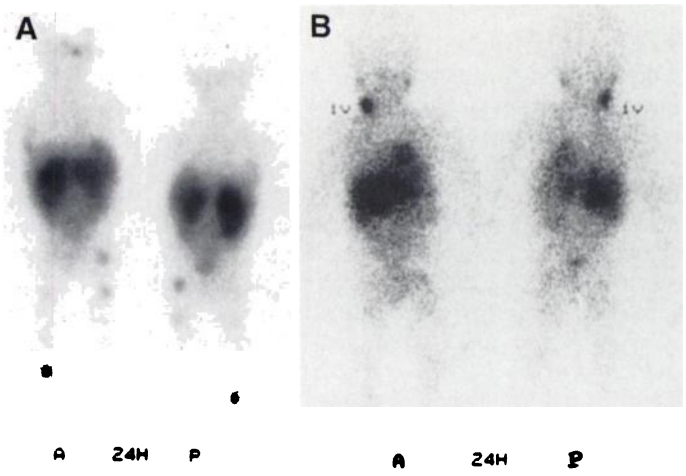

FIGURE 1. Scans from Patient 3 (Stage IVs neuroblastoma). Comparison of ^{111}In-pentetreotide (A) and [^{123}I]MIBG (B) whole-body scans. Bone marrow metastases are well depicted with ^{111}In-pentetreotide, whereas the MIBG scan is inconclusive. Liver images are blurred with both tracers. Pentetreotide uptake in the left ethmoid and suborbital areas probably corresponds to other tumor sites (confirmed by a second scan 3 wk later), but a common rhinitis cannot be completely excluded. A = anterior; P = posterior; iv = site of injection.

sponding to ^{111}In-pentetreotide-positive spots). Patient 5 had a relapse in the bone marrow 2 yr after primary treatment; his unique skull metastasis concentrated both tracers (the ^{111}In-pentetreotide image was far better). The right femur metastasis was clearly identified by ^{111}In-pentetreotide but appeared only as a doubtful blurred area with MIBG, not separable from the muscle background (Fig. 2). This spot corresponded to a well-known residual "sleeping" metastasis.

Two of the 3 patients with negative results had true-negative results (Patients 7 [ganglioneuroma] and 11 [Stage III]), as determined at general exploration (MIBG, bone scan, bone biopsies, CT scan, ultrasound) and follow-up visit. Patient 2 (ganglioneuroblastomas, Stage IIIb) had a postsurgical abdominal mass that was visible on ultrasound in the region of the pancreatic head, but there was no sign of progression, no MIBG uptake and no abnormal urinary catecholamine levels.

For Patients 1, 4, 6 and 8–10, better defined images were obtained with MIBG than with ^{111}In-pentetreotide. In Patients 1, 4 and 8, the clinical information provided by ^{111}In-pentetreotide scans was similar to that of MIBG, whereas MIBG detected more tumors in Patients 6, 9 and 10.

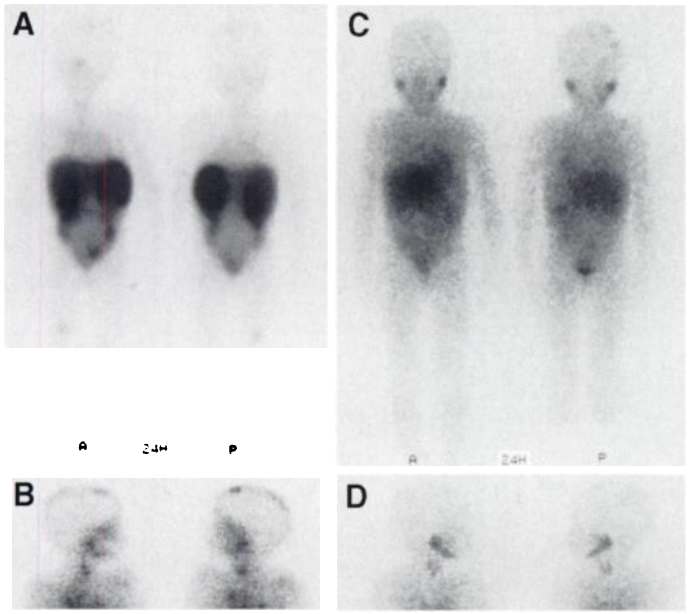

FIGURE 2. Scans from Patient 5 (Stage IV neuroblastoma). Comparison of ^{111}In-pentetreotide (A, B) and [^{123}I]MIBG (C, D). A and C, anterior (A) and posterior (P) whole-body scans. B and D, lateral views of the head. The MIBG images show a doubtful residual focus in the anterior part of the left parietal bone. Pentetreotide images show distinct foci in the right femur and left parietal bone.

Clinical Characteristics

Relevant patient characteristics were also evaluated in relation to the imaging results (Table 1).

Histological Differentiation. Three of the four ^{111}In-pentetreotide-positive primary tumors were undifferentiated (neuroblastomas). Bone marrow metastases were strongly positive in the Stage IVs neuroblastoma (Patient 3) and in one Stage IV neuroblastoma (Patient 5), moderately labeled (although distinctly) in three other Stage IV neuroblastomas and very weakly labeled in the three metastatic ganglioneuroblastomas.

Urinary Catecholamine Levels. All patients with moderately positive or very positive ^{111}In-pentetreotide scan results had pathological urinary catecholamine levels at the time of scanning (Patients 1, 3, 4, 5, 8, 10 and 11). Three patients with normal catecholamine levels (Patients 2, 6 and 7) had ^{111}In-pentetreotide-negative or borderline images. Only one patient (Patient 9) had borderline (±) ^{111}In-pentetreotide scan results together with elevated urinary catecholamine levels.

Ploidy. The ploidy profile of tumor cells was available in only five patients. The two aneuploid tumors displayed strikingly positive scan results, especially the metastases (Patients 3 and 5). The three diploid tumors exhibited less positive results (Patients 7 and 8), except for the primary tumor in Patient 1.

Gene Amplification. Nmyc gene amplification was present in a single tumor (Patient 11), which was an ^{111}In-pentetreotide-positive primary tumor.

Bone Marrow Studies. Bone marrow cytological and immunocytological and bone histologic study results were positive in six patients (corresponding to one very positive, three moderately positive and two weakly positive ^{111}In-pentetreotide bone marrow scan results) and negative in five (corresponding to one very positive, one moderately positive and 3 weakly positive ^{111}In-pentetreotide bone marrow scan results).

Follow-Up. All patients but one are still alive (complete remission in five, stable disease in four, relapse in one). It was not possible, on the basis of ^{111}In-pentetreotide image positivity, to predict, even retrospectively, which patients would be future complete responders. The 21–34-mo follow-up period was not sufficient to correlate imaging data with the long-term course of the disease nor with survival. Patient 1 had a relapse 26 mo after scintigraphy. Patient 11 died 3 mo after diagnosis, despite the absence of metastasis: his primary tumor was ^{111}In-pentetreotide positive.

Repeat Scans. In the two patients who had a second ^{111}In-pentetreotide scan, respectively, 20 days (Patient 3) or 5 mo (Patient 6) after the first, no differences were observed between the two successive studies.

Statistical Analysis. Statistical analysis is meaningless in a series of 11 patients. However, on the basis of these preliminary results, positive ^{111}In-pentetreotide scintigraphic results do not seem to be related to parameters, such as the site of the primary tumor or its presence or absence at the time of scanning, nor to current or previous chemotherapy.

DISCUSSION

Few results have been released regarding ^{111}In-pentetreotide imaging in neuroblastoma, and the possible relation with histolog-

ical differentiation has, to our knowledge, never been explored. A likely reason is that MIBG scanning is very effective and is considered by many investigators to be the reference standard, with a specificity of 98%–100% and a sensitivity close to 92% for bone marrow metastases (*16–19*). However, 5% of progressive tumors are not depicted by MIBG and could be amenable to alternative procedures. It is worth noting that some MIBG spots can persist for years in patients without apparent change in disease status. A method able to predict a relapse in these patients would be of major clinical importance.

Our preliminary results demonstrate that abnormalities detected on ^{111}In-pentetreotide images were slightly different from those seen with MIBG, especially for bone marrow. In the majority of cases, however, ^{111}In-pentetreotide images of tumors were similar to those of MIBG, with limited variations in contrast and definition, except in the renal area, where MIBG was definitely superior. The ^{111}In-pentetreotide images provided additional information in two patients, compared with MIBG scans. The quality of ^{111}In-pentetreotide images of the lower limbs was particularly good (high contrast). In the other cases, information was similar or poorer in quality with ^{111}In-pentetreotide, which means that this new imaging modality will not replace MIBG because the latter is widely available and benefits from more than a decade of clinical experience worldwide. The variable ^{111}In-pentetreotide results observed in neuroblast-derived tumors could be related to a quantitative or qualitative difference, or both, in the expression of specific receptors by different tumors. Indeed, ^{111}In-pentetreotide receptor subtypes vary in proportion, and pentetreotide is known to recognize subtype II electively (*1*).

Our comparative results differ slightly from those published by Dörr et al. (*15*) in nine children with neuroblastoma: Eight patients had both positive ^{111}In-pentetreotide and MIBG scan results, with no significant differences between these tracers, and the ninth patient had negative results with both procedures, despite obvious clinical signs of progression. In this series, the prognosis seemed to be strongly correlated with the presence of somatostatin receptors because all patients with positive ^{111}In-pentetreotide results survived, whereas all those with negative results died within a few months. Our patients had a higher proportion of differentiated tumors (four ganglioneuroblastomas and one ganglioneuroma) and slowly progressing or stable tumors, and there was some uncertainty regarding disease status because of inconclusive or long-term positive MIBG results in the absence of clinical evidence of disease.

Our series was too small to allow statistically relevant conclusions. However, some observations should be emphasized. First, ^{111}In-pentetreotide uptake was higher in neuroblastoma than in ganglioneuroblastoma. Moreover, the only ganglioneuroma was barely detected with ^{111}In-pentetreotide. For other malignancies, positivity rates are frequently higher in well-differentiated tumors, which does not seem to be the case in neuroblast-derived tumors. In neuroblastoma, however, a longer survival has been reported in patients with somatostatin receptor-positive tumors (*1,15*). Second, the best ^{111}In-pentetreotide images of metastases were observed in the two patients with aneuploid primary tumors. Ploidy should be explored in a larger number of patients to determine whether a correlation exists between this parameter and somatostatin receptor expression. Third, positive results, as expected, did in fact correspond to patients with elevated urinary catecholamine levels.

CONCLUSION

Indium-111-pentetreotide imaging of neuroblast-derived tumors provided information different from and most likely complementary to that of MIBG. However, in view of our results, [^{123}I]MIBG, whose uptake mechanism is theoretically more specific for neuroblast-related cells and provides better images of the adrenal region (low kidney uptake) and, in many cases, of bone marrow metastases, is still often superior. In the two patients in whom ^{111}In-pentetreotide depicted lesions that had been missed or only appeared doubtful with MIBG, histological confirmation (immunohistochemical analysis of somatostatin receptors is not presently available) would assess whether such foci actually correspond to active tumor cells or, in certain cases, to "activated" lymphocytes, as observed in lymphoma and various inflammatory diseases (*1,10*). A tumoral origin is very likely because the ^{111}In-pentetreotide-positive foci actually correspond to MRI-positive spots in Patient 3 and to formerly positive MIBG results in Patient 5. Prediction of response to treatment with ^{111}In-pentetreotide imaging also remains inconclusive and could be the goal of further studies, with a larger number of patients and a longer follow-up period. The degree of specificity of ^{111}In-pentetreotide scans and the clinical significance of ^{111}In-pentetreotide uptake by certain but not all tumor foci (related to the number or subtypes of receptors) will determine the future of this new imaging modality in neuroblastoma.

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