High risk of myelodysplastic syndrome and acute myeloid leukemia after ^{177}Lu-octreotate PRRT in NET patients heavily pretreated with alkylating chemotherapy

Dear Editor,

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare but seen with increasing incidence. Current medical options for the management of nonresectable GEP-NETs include somatostatin analogs, targeted therapies, chemotherapies, and radiological and radionuclide therapies.

Peptide receptor radionuclide therapy (PRRT) is a modern therapeutic approach using radionuclide combined with somatostatin analog peptide whose affinity with somatostatin receptors (SSRs) allows targeting disseminated tumor disease. According to the ENETS guidelines, PRRT is indicated for patients with nonresectable, progressive, grade 1 or 2 GEP-NETs with high uptake on SSR scintigraphy (Pavel *et al.* 2012). In a large retrospective study of 310 GEP-NETs, 46% had tumor response with ^{177}Lu-octreotate therapy (Kwekkeboom *et al.* 2008) with good progression-free and overall survival. In addition, first results of the prospective randomized NETTER-1 trial comparing ^{177}Lu-octreotate PRRT and octreotate LAR 60 mg have recently showed a median progression-free survival not reached at 25 and 8.4 months, respectively (Strosberg *et al.* 2015). PRRT is generally well tolerated, short-term side effects include mild fatigue, hematological and renal toxicity. Regarding longer term hematological side effects, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) was reported in 0.2–5.4% of the patients in large series (Kwekkeboom *et al.* 2008, Imhof *et al.* 2011, Sabet *et al.* 2013, Kesavan *et al.* 2014, Bodei *et al.* 2015). Here, we report a much higher occurrence of MDS or AML in a single-center experience in patients treated with ^{177}Lutetium-octreotate at late disease stage, after alkylating-based chemotherapy.

Our study included all 20 consecutive patients treated with ^{177}Lutetium-octreotate PRRT between January 2004 and January 2011 at our center. All patients had progressive metastatic GEP-NETs. PRRT was performed in the Department of Nuclear Medicine of the Erasmus Medical Center of Rotterdam (Rotterdam, the Netherlands) due to the unavailability of PRRT in France. This unavailability explained why relatively few patients received this treatment in our center, and generally after first-line chemotherapy. As defined in previous reports from Rotterdam's team (Kwekkeboom *et al.* 2001), the radiochemical purity of ^{177}Lu-octreotate was 88%, and then reached yield after addition of DTPA (diethylenetriaminepentaacetic acid) approached 99.99%. Patient medical records were reviewed to collect relevant data on demographics, tumor characteristics, surgery, treatments, and tolerability. A Student's t-test was used to evaluate prognostic variables for the occurrence of therapy-related MDS or AML (t-MDS/AML).

Baseline clinical characteristics of the 20 patients are described in Table 1. Median follow-up from PRRT was 3.1 years (range 0.3–8.9). Treatment with ^{177}Lu-PRRT consisted of four cycles of 7.5 GBq; 16 patients received the four full dose cycles (one of them received two additional cycles) and 4 received lower dose due to early hematological toxicity (one of them one cycle).

PPRT induced short-term thrombocytopenia, neutropenia, and anemia in 25, 15, and 10%, respectively. However, four (20%) patients developed

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delayed hematological toxicity with MDS or AML, diagnosed 30, 31, 54, and 70 months, respectively, after PRRT. All patients, before PRRT, had received prior chemotherapy containing an alkylating agent for 20, 12, 6, and 12 cycles, respectively. Three of the four patients (75%) had developed early hematological toxicity (grade 3–4 thrombocytopenia) during PRRT. At the time of MDS/AML diagnosis, the underlying tumor was active in three patients, and three had bone metastases. Three patients had MDS according to the WHO criteria (Della Porta *et al.* 2015), including refractory cytopenia with multilineage dysplasia in two cases, and refractory anemia with excess blasts type 2 in one case; the last patient had the WHO-defined AML (with, however, only 21% marrow blasts, i.e., partial blast infiltration very close to MDS diagnostic criteria). Karyotype showed monosomy 7 in three cases, with or without other chromosomal deletions, especially monosomy 5, and was not performed in the last patient.

Compared to other patients, the four patients who developed MDS or AML had received, prior to PPRT, more cycles of chemotherapy (mean: 13.8 vs 4.7, $P=0.001$) and more cycles of alkylating agents (mean: 12.5 vs 3.75, $P=0.001$), and had more frequently experienced early hematological toxicity (75 vs 13%, $P=0.03$) (Table 2). Two of the patients received supportive care only and two received azacitidine. Survival was 6, 2, 2, and 54 months, respectively. During the study period (2004–2011), 95 additional patients with GEP-NETs were treated with alkylating-based chemotherapy without subsequent PPRT at our center. Only one (1%) developed MDS.

The high rate of MDS or AML (20%) we report in this limited series of 20 nonresectable NETs treated with ^{177}Lu-PPRT after heavy pretreatment with chemotherapy is therefore much higher than in large published series of PRRT (Kwekkeboom *et al.* 2008, Imhof *et al.* 2011, Sabet *et al.* 2013, Kesavan *et al.* 2014, Bodei *et al.* 2015). This higher rate may be due to the fact that most of our patients had received chemotherapy and alkylating agents prior to PPRT, compared to previously published series of PPRT in metastatic NETs, where less than one-third of the patients had received chemotherapy before PRRT. Indeed, in our series, patients who developed MDS or AML had received more chemotherapy and more alkylating agents than other patients ($P=0.001$). Reasons why patients had received more chemotherapy prior to PRRT in our series probably include the fact that PPRT was until recently unavailable in France, requiring a partnership with centers abroad. Thus, PRRT was not a frontline therapy for metastatic GEP-NETs in France, where patients first received conventional systemic chemotherapy, targeted therapies, and transarterial chemoembolization.

In another study, about 65 patients receiving ^{177}Lu-octreoate combined with capecitabine ($n=28$) or capecitabine and temozolomide ($n=37$), no MDS/AML was reported in the former group, but two (5.4%) cases were reported in the latter group (Kesavan *et al.* 2014). Temozolomide is an alkylating agent, further supporting our assumption that the risk of MDS/AML, very low with ^{177}Lu-octreotate PRRT alone and possibly ^{177}Lu-octreotate PRRT combined with nonalkylating chemotherapy, may be higher when ^{177}Lu-octreotate PRRT is combined with alkylating agents.

The duration of follow-up in our series (3.1 years) cannot explain differences of MDS/AML rates compared with other studies: indeed, although three studies had shorter follow-up (1.6, 1.9, and 2.6 years) (Kwekkeboom *et al.* 2008, Imhof *et al.* 2011, Sabet *et al.* 2013), two other studies had similar or longer follow-up (3.0 and 4.2 years) (Kesavan *et al.* 2014, Bodei *et al.* 2015). Because of the known leukemogenic role of alkylating agents, we cannot exclude that MDS/AML in our series was a direct consequence of prior chemotherapy. Indeed, latencies before the first cycle of chemotherapy, and the diagnosis of the hematological malignancies were 12.6, 9.8, 3.8, and 10.4 years, respectively. It is well known that the maximum risk of MDS/AML ranges from 3 to 10 years after the myelotoxic treatment. However, the risk of MDS/AML in GEP-NETs treated with alkylating-based chemotherapy alone may be relatively small: during the study period (2004–2011), 95 additional GEP-NETs patients were treated with this approach without subsequent PPRT at our center, and only one (1%) developed MDS.

Other risk factors for MDS/AML, in our study, included early hematological toxicity after PPRT, observed in 3 of the 4 patients who subsequently developed MDS/AML, compared to only 2 of the 16 patients who did not develop MDS/AML. Platelet toxicity was also significantly related to development of secondary MDS or AML in a previous study (Bodei *et al.* 2015): close hematological monitoring therefore seems recommended in patients experiencing early hematological toxicity after PRRT. MDS and AML cases observed in this series were typical of those observed after alkylating agents or purine analogs. Indeed, they all had partial marrow blast infiltration (maximum 21%) and the three karyotyped patients had monosomy 7.

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Table 1 Patients' characteristics

Patient, age at diagnosis	**Type of tumor, ENETS grade** (G1/G2/G3)	**Treatments before PRRT: time interval from diagnosis, type of treatment (number of cycles), and response**	**Hematological toxicities of each treatment**	**Number of CT cycles and the time from the first cycle to PRRT** (months)	**Bone metastases** (localization)	**Bone metastases** (metabolic burden)*	**PRRT: number of cycles, total dose (Gbq), and tumor response** (CR/PR/SD/PD)	**AHT of PRRT, duration** (months)	**DHT**
N° 1, 45	Pancreatic NET, G1	S at 2 months: left pancreatectomy with complete resection	None	25, 121 months	Left ischial tuberosity and occipital part of the skull	G2	4, 29.9, PR	None	Yes
		CT at 54 months: streptozotocin + adriamycin + interferon (9), PR	G2 NE, G1 TH						
		TACE at 75 months: streptozotocin (3), SD	None						
		S at 115 months: liver transplantation	None						
		CT at 116 months (adjuvant): 5-fluorouracile + streptozotocin (4), SD	None						
		RT at 160 months (hip and skull bones): clinical response	None						
		CT at 163 months: 5-fluorouracil + streptozotocin (4), PD	None						
		CT at 170 months: FOLFIRI regimen (5), SD	None						
N° 2, 54	Pancreatic NET, G1	CT at 4 months: 5-fluorouracil + streptozotocin (8), SD	None	12, 47 months	None	G0	4, 29.9, CR	G3 TH, G1 AN, 12 months	Yes
		CT at 54 months: adriamycin + dacarbazine (4), SD	None						
N° 3, 66	Metastatic NET with unknown primary, G1	CT at 6 months: 5-fluorouracil + streptozotocin (6), SD	None	6, 15 months	Disseminated metastases of the spine, sternum, ribs, and bony pelvis	G4	4, 26.5, PR	G3 NE, G4 TH, G1 AN, 12 months	Yes
N° 4, 50	Gastric NET, G2	TACE at 4 months: streptozotocin (4), PR	None	12, 71 months	Thoracic vertebrae (second and seventh)	G0	4, 30, CR	G3 NE, G3 AN, G3 TH, 54 months	Yes

(Continued)

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Table 1 (*Continued*)

Patient, age at diagnosis	**Type of tumor, ENETS grade** (G1/G2/G3)	**Treatments before PRRT: time interval from diagnosis, type of treatment (number of cycles), and response**	**Hematological toxicities of each treatment**	**Number of CT cycles and the time from the first cycle to PRRT** (months)	**Bone metastases** (localization)	**Bone metastases** (metabolic burden)*	**PRRT: number of cycles, total dose (Gbq), and tumor response** (CR/PR/SD/PD)	**AHT of PRRT, duration** (months)	**DHT**
		CT at 34 months: 5-fluorouracil + dacarbazine (4), SD	None						
		S at 48 months: liver transplantation	None						
		CT at 50 months (adjuvant): 5-fluoro-uracil + streptozotocin (4), SD	None						
N° 5, 37	Rectal NET, G2	TACE at 2 months: streptozotocin (1), SD	None	1, 6 months	Cervical vertebrae, left iliac wing	G1	4, 25.75, PR	G2 AN, G3 TH, G1 NE, 18 months	No
N° 6, 49	Pancreatic NET, G2	CT at 3 months: FOLFIRI regimen (10), PR	None	19, 32 months	Two lumbar vertebrae, sacrum	G2	1, 7.5, SD	G4 AN, G4 TH, G4 NE, 5 months	No
		CT at 22 months: etoposid + cisplatin (4), PD	None						
		CT at 25 months: sunitinib (5), SD	G2 NE						
N° 7, 68	Rectal NET, G2	TACE at 3 months: streptozotocin (3), SD	None	3, 11 months	Disseminated metastases of the spine and ribs	G3	6, 45, PR	None	No
N° 8, 69	Rectal NET, G2	S at 1 month: rectal resection with coloanal anastomosis	None	9, 21 months	Disseminated metastases of the spine and ribs	G3	4, 30, PR	None	No
		CT at 70 months: 5-fluorouracil + dacarbazine (8), SD	None						
		TACE at 83 months: Streptozotocin (1), PR	None						
N° 9, 59	Ileum NET, G1	S at 1 month: right ileocolectomy	None	4, 21 months	None	G0	4, 30, SD	None	No
		CT at 43 months: 5-fluorouracil + streptozotocin (4), PD	None						
N° 10, 64	Ileum NET, G1	S at 1 month: segmentary resection of the ileum tumor	None	0	None	G0	4, 30, PD	None	No

N° 11, 61	Pancreatic NET, G1	None		0	None	G0	4, 30, CR	None	No
N° 12, 71	Pancreatic NET	None		0	None	G0	4, 30, PR	None	No
N° 13, 46	Pancreatic NET, G2	S at 2 months: cephalic duodenopancreatectomy	None	0	None	G0	4, 30, PR	None	No
N°14, 53	Ileum NET, G2	S at 1 month: segmentary resection of the ileum tumor	None	0	Left scapula and right hip	G2	4, 30, PR	None	No
N° 15, 47	Ileum NET, G1	CT at 12 months: 5-fluorouracil+streptozotocin (2), SD	None	2, 9 months	None	G0	4, 30, PR	None	No
N° 16, 55	Colon NET, G1	S at 1 month: resection of the primary tumor	None	0	One thoracic vertebrae	G1	4, 30, CR	None	No
N° 17, 26	Duodenal NET, G2	S at 1 month: cephalic duodenopancreatectomy	None	8, 12 months	Disseminated metastases of the spine	G3	4, 30, SD	None	No
		CT at 8 months: adriamycin+streptozotocin (4), PD	None						
		CT at 15 months: FOLFIRI regimen+bevacizumab (4), PD	None						
N° 18, 16	Pancreatic NET, G1	S at 1 month: left pancreatectomy	None	6, 131 months	Sacrum and right hip	G1	4, 30, PR	None	No
		S at 8 months: right hepatectomy	None						
		CT at 10 months (adjuvant): adriamycin+streptozotocin (6), SD	None						
		S at 51 months: liver resection	None						
N° 19, 31	Anus NET, G2	S at 1 month: abdominoperineal resection	None	4, 12 months	None	G0	4, 30, PR	None	No
		CT at 121 months: 5-fluorouracil+dacarbazine (4), PD	None						
N° 20, 64	Pancreatic NET, G2	CT at 2 months: etoposid+cisplatin (6), SD	G3 NE	19, 18 months	None	G0	3, 22.5, PD	None	No
		CT at 10 months: FOLFIRI regimen (13), PR	G2 NE						

Abbreviations: AHT, acute hematological toxicity; AN, anemia; CR, complete response; CT, chemotherapy; DHT, delayed hematological toxicity; FOLFIRI, 5-fluorouracil+leucovorin+irinotecan; G1, grade 1; G2, grade 2; G3, grade 3; NE, neutropenia; NET, neuroendocrine tumor; PD, progressive disease; PR, partial response; PRRT, peptide receptor radionuclide therapy; RT, radiotherapy; S, surgery; SD, stable disease; TACE, tranzarterial chemoembolisation; TH, thrombopenia.

Tumor aggressiveness was evaluated according to the ENETS grade (Ki-67 proliferative index): G1, tumor with Ki-67 from 0 to 2%; G2, Ki-67 from 3 to 20%; G3, Ki-67 superior than 20%.

*Bone involvement is graded according to the results of the OctreoScan. G0, no metastases; G1, 1–5 bone uptakes; G2, 6–10 bone uptakes; G3, more than 10 bone uptakes with disseminated spine involvement; G4, G3 and bone marrow involvement.

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Table 2 Prognostic factors of occurrence of MDS and AML in patients treated with PRRT

	Patients who developed MDS/AML, *n* (%)	Other patients, *n* (%)	*P*-value
Total	4 (20)	16 (80)	
Gender (F/M)	3 (75)	4 (25)	0.16
Median age at diagnosis (years) (range)	53.8 (45–66)	51 (16–71)	0.63
Mean number of cycles of previous chemotherapy (range)	13.8 (6–25)	4.7 (0–19)	**0.001**
Alkylating-based chemotherapy mean number of cycles (range)	12.5 (6–20)	3.75 (0–9)	**0.001**
Bone metastases before PRRT	3 (75)	8 (50)	0.39
Immunosuppressive treatment	2 (50)	0 (0)	**0.006**
Mean dose of PRRT (GBq)	29	30.5	0.94
Mean number of cycles of PRRT	4	4	0.97
Early hematological toxicity grade 3–4	3 (75)	2 (13)	**0.03**
Number of deaths	4 (100)	4 (29)	–
Cause of deaths: underlying tumor	0 (0)	4 (29)	–
MDS/AML	4 (100)	0 (0)	–

Abbreviations: AML, acute myeloid leukemia; F, female; M, male; MDS, myelodysplastic syndrome; PRRT, peptide receptor radionuclide therapy. Bold indicates significant values.

The impact of bone metastases in the occurrence of MDS/AML remained unclear, and it had no significant impact in our study (P=0.39). In a pilot study in 11 patients with GEP-NETs and florid bone metastases (with advanced widespread metastatic bone disease) receiving PRRT (Sabet *et al.* 2014), a higher than usual rate of hematological toxicity was reported, with grade 3–4 reversible hematotoxicity of in 35% of the patients, but delayed hematological toxicity was not reported. In other studies, no statistical correlation between bone metastases after PRRT and the recovery of acute hematotoxicity or the subsequent occurrence of MDS/AML was seen (Sabet *et al.* 2013, Bergsma *et al.* 2015).

In conclusion, our study, although based on a limited number of patients, suggests a high occurrence of MDS/AML in patients with GEP-NETs treated with PRRT after previous chemotherapy with alkylating agents. The indication of PRRT should take into consideration the importance of previous chemotherapy. Exposure to alkylating agents should be avoided in patients with low-grade NET, who have a long survival expectancy and a significant likelihood of benefiting from PRRT, because it may compromise the safety and future applicability of this more effective therapy. Regular and prolonged monitoring of blood counts is mandatory, especially in patients experiencing early hematological toxicity after PRRT.

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