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LETTER TO THE EDITOR

# Secondary acute myeloid leukaemia after peptide receptor radionuclide therapy

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Dear Editor,

Peptide receptor radionuclide therapy (PRRT) with $^{90}$Y-DOTATOC or $^{177}$Lu-DOTATATE has demonstrated its efficacy in the treatment of neuroendocrine- and somatostatin-receptor expressing tumours [1, 2]. Several clinical trials have confirmed that adverse effects are represented by possible renal impairment [3] and low but not absent haematological toxicity.

We report on a patient who developed acute myeloid leukaemia (AML) following peptide receptor radionuclide therapy for a well-differentiated neuroendocrine carcinoma.

He was a 50-year-old man with a past medical history of alcoholism, oesophagitis, arterial hypertension, thalassemia β-minor and deep venous thrombosis of left popliteal vein. He was also a heavy smoker. In November 2005 following repeated episodes of upper abdominal pain, he underwent a thoracic and abdominal CT-scan which showed a pancreatic lesion of 20 mm and another lesion in the Vater papilla of 30 mm in size. An Octreoscan® showed high uptake on the upper right renal pole and on the fifth and seventh hepatic segments. An oesophagoduodenoscopy revealed a duodenal neoformation of 20 mm. The ampullary lesion and peri-pancreatic lymph node were surgically removed in April 2006, and a fine needle biopsy of the liver was performed.

Histology of the ampullary lesion showed a low-grade neuroendocrine carcinoma with extension to the duodenal submucosa, mucosa and focal angioinvasion. Immunohistochemistry was positive for chromogranin A, synaptophisin, neuron-specific enolase and for cytokeratins AE1–AE3 focally. Ki67 was expressed in less than 1% of nuclei. Insulin and glucagone himmunoistochemistry was negative. Histology of the lymph node demonstrated metastasis of the neuroendocrine carcinoma, whereas the liver biopsy showed necrosis without vital tumour cells.

Between November 2005 and June 2007, the patient was closely monitored by repeated abdominal CT-scans. In October 2006 an Octreoscan® was repeated on the patient which showed a focal uptake in the pancreatic region. In June 2007, two new small suprarenal lesions were detected; the peri-pancreatic lesion was unchanged. On the basis of the neuroendocrine carcinoma and the increased uptake in receptor scintigraphy, the patient was started on PRRT. From June 2007 to February 2009, he received 6 cycles of PRRT with a cumulative activity of 20.16 GBq (545 mCi) of $^{177}$Lu-DOTATATE and 5.55 GBq (150 mCi) of $^{90}$Y-DOTATOC. A CT scan performed in October 2008 after 2 cycles of PRRT showed no increase in the size of peri-pancreatic and surrenalic lesions. This finding was confirmed by a subsequent CT-scan in January 2009. The patient completed his PRRT treatment in February 2009. A follow-up CT-scan performed in December 2009 documented that the disease was stable.

In January 2010 pancytopenia was observed with Hb 9.1 g/dl, white cell count 6,400/μl, neutrophils 70% and platelets 157,000/μl. A bone marrow aspirate showed hypocellularity with trilineage dysplasia and blasts count <5%, suggestive of alcohol-induced myelodysplastic syndrome

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(MDS). Cytogenetic study showed 46XY, FISH study for MDS was negative. A re-evaluation of the bone marrow aspirate in April 2010 showed no changes. However, in September 2010, a full blood count showed Hb 7.9 g/dl, white cell count 2,460/μl, neutrophils 20% and platelets 94,000/μl, a blood smear revealed 13% blasts. A bone marrow aspirate confirmed the presence of AML M2 diagnosis. Cytogenetic investigations showed 46,XY,der(3)t(3;7)(q22;q11.2),-7,+i(11)(p10)[12]/46,XY [4]. The patient was randomised in the NILG-AML 02/06 and immediately started on chemotherapy regimen with ICE schedule (idarubicin 12 mg/m$^2$ on days 1–3, etoposide 100 mg/m$^2$ BD on days 1–5, and cytarabine 100 mg/m$^2$ BD on days 1–7). However, on day +16, a bone marrow aspirate showed 50% blasts. A salvage chemotherapy cycle with HDS 3/2 schedule (idarubicin 17.5 mg/m$^2$ on days 3 and 10, cyclosporin A 6 mg/kg on day 3 and 7.5 mg/kg on day 10, cytarabine 3 g/m$^2$ BD on days 1, 2, 8, and 9) was attempted, however the patient died on day +52 due to leukaemia progression.

MDS has already been reported with [$^{111}$In-DTPA]-octreotide and $^{90}$Y-DOTATOC; however, these patients were previously treated with chemotherapy so it was not possible to find a direct link between PRRT and bone marrow dysplasia/leukaemia [5]. A transient lymphocytopenia with selective B-cell depletion but without clinical impact has also been reported after $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE administration [6]. Recently, Merola and colleagues reported on a case of acute lymphoblastic leukaemia (ALL) following treatment with 7.68 GBq of $^{90}$Y-DOTATOC in 3 cycles [7]. The onset of ALL was immediately after the third cycle of PRRT, suggesting a pre-existing haematological alteration and not a direct correlation between PRRT and leukaemia.

On the contrary, the case reported here is suggestive of a possible link between peptide receptor radionuclide therapy and secondary acute leukaemia (AML), if we consider that the patient did not receive other myelotoxic therapies, and there was a longer time interval before the onset of the leukaemia. Moreover, our patient had several cytogenetic abnormalities and monosomy 7, typically found in MDS→AML. The finding of a complex cytogenetic damage supports the idea of a drug-induced leukaemia [8]. However, we have to consider that the bone marrow of this patient was probably already damaged by years of other toxic factors, such as alcohol abuse and heavy smoking. Moreover, this patient was affected by thalassemia β-minor and received periodic radiological examination that could have contributed to the bone marrow irradiation and could in turn have favoured the progression towards leukaemia.

In view of the increasing interest and use of PRRT in neuroendocrine tumours, due to its promising treatment results and mild global toxicity, more attention should be given to those patients with significant risk factors, as in this case report, in order to decrease potential late side effects. In PRRT the kidney irradiation is a constant; haematological toxicity, although low, needs to be monitored. So, in this context, a personalised dosimetry should always be performed when planning therapy with radiopeptides [4]. Individual patient variables such as biodistribution, tumour uptake, risk factors and social behaviours must be taken into account in order to tailor the therapy and avoid unnecessary side effects.

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