Somatostatin analogs in pregnant patients with neuroendocrine tumor

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Somatostatine analogs (SSAs) are currently indicated in the treatment of acromegaly and neuroendocrine tumors (NETs). Actually, pregnancy in patients with acromegaly and NETs does not represent an exceptional event because reproductive behavior has changed in the last decades and patients with NETs show more frequently long-term survival. The safety profile of SSAs during pregnancy is still controversial. Concerning acromegaly, based on case reports and series, SSAs administration during pregnancy seems to be relatively well tolerated. Concerning patients with NETs, up to date only one patient with NET receiving SSA during pregnancy has been reported in literature. We report two cases of gastroenteropancreatic-NET patients receiving SSA lanreotide for the entire course of their pregnancy, with favorable outcomes for both mothers and babies. Our experience supports the possibility to continue safely SSA lanreotide during pregnancy in patients with NET. ***Anti-Cancer Drugs*** **31: 1096–1098**

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Introduction

Somatostatine analogs (SSAs) are currently indicated in the treatment of endocrinologic and oncologic diseases, namely acromegaly (pasireotide) [1] and neuroendocrine tumors (NETs) (octreotide and lanreotide) [2]. Acromegaly is characterized by over secretion of growth hormone and because SSAs are able to inhibit growth hormone secretion, they represent the treatment of choice [3]. In functioning NETs, SSAs are the standard of care for syndrome control [4–6]. For tumor growth control, antiproliferative effects of SSAs are described [7,8] and there is consensus that SSA can be used as first-line therapy in gastroenteropancreatic NETs (GEP-NETs) [9,10]. In particular, CLARINET trial has demonstrated that lanreotide, compared with placebo, significantly prolonged progression-free survival (PFS) among patients with metastatic GEP-NETs (median not reached vs. median of 18.0 months) [9]. Recently, an interim analysis of the CLARINET extension study confirmed sustained antitumor effects with lanreotide in metastatic GEP-NETs (median PFS 38.5 months, 95% confidence interval, 30.9–59.4) [10].

Nevertheless, progress has been made in the therapeutic management of acromegaly and NETs, as a consequence, even patients affected by advanced NET achieve definitely long-term survival. Moreover, reproductive behavior has changed in the last decades: the age at first pregnancy increased and improvements in assisted reproductive techniques occurred. Therefore, pregnancy in patients with acromegaly and NETs does not represent an exceptional event.

Referring to our experience, two pregnant patients with GEP-NETs treated with SSA lanreotide during pregnancy were followed at the Medical Oncology Unit, Azienda Ospedaliero Universitaria (AOU) Careggi (Florence, Italy). To date, no published data of pregnant patients with GEP-NET receiving SSAs throughout pregnancy have been reported.

Cases description

Case 1

A.E. is a 41-year-old overweight Nigerian woman, with refractory hypertension and chronic hypertensive heart disease. In September 2015, she was diagnosed with nonfunctioning ileal NET G2 (Ki67 4%), with breast, axillary lymph nodes and liver metastases. In March 2016, she started SSA lanreotide depot 120 mg, monthly injection. In July, she was found to be 12 weeks pregnant by urine human chorionic gonadotropin (hCG) test. Approximately, four lanreotide doses had been administered until that time with disease stabilization. Considering the antitumor purpose of treatment (see data reported in the European Neuroendocrine Tumor

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Society Consensus Guidelines) [9] and the consulting from the Toxicology Unit of AOU Careggi, we decided to continue lanreotide. The patient was informed of the treatment and strictly controlled by the Department of Fetal and Neonatal Medicine, AOU Careggi. During the gestation period, a regular fetal development was registered and blood glucose levels have been monitored.

Unfortunately, pregnancy was complicated by gestosis with hypertensive emergency, requiring cesarean delivery at 35 weeks. The patient gave birth to a healthy baby, 2540 kg weight, 46 cm length and 8/10 APGAR score. In November 2017, the patient referred to our center for a control visit: she was in good condition, continuing lanreotide therapy, with confirmed disease stabilization. Afterwards, the patient was lost to follow-up.

Case 2

T.Y. is a 37-year-old Japanese woman diagnosed with pNET with liver and bone metastases. In July 2012, she underwent distal splenopancreatectomy and liver resections in Japan with a pathological report of NET G2, Ki67 11%, pT2N0M1 and in August 2012, the patient started therapy with SSA lanreotide depot 120 mg, monthly injection. In August 2014, the patient was found to be 8 weeks pregnant by urine hCG test. Approximately, 24 lanreotide doses had been administered until that time with disease stabilization. Lanreotide was continued and the patient delivered by elective cesarean section at 39 weeks. The patient experienced good control of blood glucose without any significant worsening and a regular fetal development was registered during the gestation period. She gave birth to a healthy baby, 3320 kg weight, 51 cm length and 10/10 APGAR score. In July 2015, after about 1 year, the patient referred to our center having experienced the progressive disease in the liver and bone. We then started therapy with everolimus 10 mg daily, which is still ongoing with SSA, with disease stabilization up to June 2019.

Discussion

For the first time, we report the use of SSA during pregnancy in two women with GEP-NETs. SSAs have been shown to be effective in the treatment of endocrinologic and oncologic diseases, such as acromegaly [1] and NETs [2,9,10]. The safety profile of SSAs during pregnancy is still controversial. Concerning patients with acromegaly, definitive evidence among the safety of SSAs is still lacking, especially considering the absence of long-term data in offsprings. Nevertheless, based on case reports and series reported in literature, SSAs administration during pregnancy seems to be well tolerated for both mother and child [11–17]. Indeed, a very low SSA binding to the placenta and umbilical cord tissues has been observed [18]. However, a systematic review by Jesu *et al.* showed that in women with acromegaly, treatment with SSA during pregnancy is associated with increased frequency of small-for-gestational-age infants, probably related to hemodynamic changes in the maternal–fetal barrier tissues [18,19]. Furthermore, SSAs are used for the management of blood glucose levels in expectant hyperinsulinemic mothers and literature evidence exists that octreotide may pose a risk of fetal growth restriction [20,21]. For this reason, pregnancy with hyperinsulinism represents a medical dilemma. Conversely, SSA treatment can be safely withdrawal in most pregnant patients with acromegaly previously treated with surgery or radiotherapy [20,21]. Possible fetal neurotoxicity cannot be excluded when SSA is administered during pregnancy because fetal neurogenesis seems to be supported by maternal serotonin levels in the mouse model [22].

Referring to SSA administration during pregnancy in patients with NETs, it is a challenging decision if to continue or not the hormonal therapy. A relevant challenge is represented by the management of the eventually associated carcinoid syndrome and the potential risk of carcinoid crisis during delivery. Evidence exists that pregnant patients with NET and acromegaly patients might experience an increase in carcinoid syndrome with a significant worsening of symptoms during gestation [16].

To the best of our knowledge, only one patient with NET receiving uneventful use of SSA during pregnancy has been reported in literature: an Arabic woman with bronchial carcinoid-associated adrenocorticotropic hormone-dependent Cushing's syndrome received octreotide long-acting release (LAR) 30 mg/month during three consecutive full-term pregnancies, and all of which were uneventful and yielding healthy babies [23]. Pistilli *et al.* also reported the case of a pregnant woman with an ovarian NET, liver metastasis and carcinoid syndrome receiving octreotide LAR 30 mg every 4 weeks. However, SSA was stopped immediately after the onset of pregnancy. Nevertheless, spontaneous abortion occurred at 12 weeks [24]. Another report, by Le *et al.*, is about the management of the carcinoid syndrome in a GEP-NET pregnant patient with liver metastasis: carcinoid crisis occurred during pregnancy were resolved with long-acting octreotide. Furthermore, it was supposed that administering octreotide intravenously, combined with neuraxial analgesia/anesthesia, throughout delivery could prevent any eventual carcinoid crisis [25].

In the perspective of a progressive and deeper knowledge about the safety profile of SSA during pregnancy, it is of utmost importance that clinicians provide regulatory agencies with their feedbacks among any suspected SSA-related adverse reaction occurring during pregnancy, the delivery or the postpartum period and those possibly affecting the health of mother and child.

Finally, SSA administration in a pregnant patient with NET is still a matter of debate. SSA therapy during pregnancy seems to be reasonably well tolerated, based on limited literature data, mainly derived from case studies

of patients with acromegaly. We described here for the first time two cases of GEP-NET patients receiving SSA lanreotide for the entire course of their pregnancy. A favorable outcome was observed for both mother and child in both cases reported. To date, no previous experiences were published in literature on this specific topic. Our experience supports the possibility to continue lanreotide during pregnancy in patients with NET with a high risk of tumor progression in case of discontinuation of treatment.

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Conflicts of interest

L.A. received speakers honoraria and advisory role from Novartis and Ipsen. For the remaining authors, there are no conflicts of interest.

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