
LETTER TO THE EDITOR

Expectations of Response from Octreotide Therapy in Recurrent Phosphaturic Mesenchymal Tumors - Do They Reflect Reality?

Asian Pac J Cancer Prev, **15** (24), 10997-10998

To the Editor

Phosphaturic mesenchymal tumor (PMT) is a rare and small tumor leading to oncogenic osteomalacia and deriving mostly from benign mesenchymal origin. The tumor may originate in any part of the body such as soft tissue or bone site, but is more frequent in the upper and lower extremities and craniofacial sinuses. Its most common type is oncogenic osteomalacia (OO) associated phosphaturic mesenchymal tumor, mixed connective tissue type (Weider and Santa Cruz, 1987).

Pathological mechanisms underlying OO associated PMTs still remain unknown, but recently it has been found that these tumors express metabolically active fibroblast growth factor-23 (FGF-23) termed as phosphatonins. FGF-23 gene, which is expressed at low level in normal tissue, has a high rate of expression in these tumors (Jonsson et al., 2003). FGF-23 protein phosphate is secreted by mesenchymal tumor inhibits renal tubular epithelial absorption, which in turn results in renal phosphate wasting and developing hypophosphatemia leads to osteomalacia with bone fractures and widespread muscular weakness (Carpenter, 2003). *In-vitro* studies have demonstrated that many mesenchymal tumours express somatostatin receptors (Reubi et al., 1996). Treatment with somatostatin analogue octreotide is an alternative form of medical therapy that may be considered when the tumor cannot be found despite intensive search. In the present report, the response of a case with phosphaturic mesenchymal tumor secreting FGF-23 and associated with oncogenic osteomalacia that has been followed for 7 years to octreotide treatment is evaluated.

It is difficult to diagnose PMTs, since they are of small size, grow slowly and frequently has unusual locations, leading to delay in treatment (Jan de Beur et al., 2002). This disease courses with local recurrences and tumor resection brings about improvement of symptoms by correcting metabolic imbalance (Folpe AL., et al (2004). Positive staining was detected in a current study for somatostatin receptor in 14 PMT patients secreting FGF-23 (Houang et al., 2013). It was demonstrated that in PMTs expressing somatostatin receptors (SSTRs), whole-body Tc-octreotide scintigraphy with SPECT/CT can demonstrate occult oncogenic osteomalacia (Rodrigues et al., 2014). In 6 patients whose diagnosis was delayed in spite of serious symptoms, gallium-68 DOTATATE PET/CT detected localized phosphaturic mesenchymal tumors

successfully and it was suggested that it can be used in the first stage in this disease (Clifton-Bligh et al., 2013). Early diagnosis may minimize the unfavorable outcome of osteomalacia.

Data on the treatment of mesenchymal tumors associated with oncogenic osteomalacia is limited. Nevertheless, as clinical, biochemical and radiological characteristics of this disease are similar to those of X-linked disease, analogous treatment regimens (including of a combination of vitamin D, calcium, and/or phosphate supplementation) can be used. Treatment should be maintained until surgical removal of the tumor. Biochemical abnormalities and symptoms of the patient resolve rapidly with removal (Jan de Beur, 2005).

It has been proposed that in cases in whom somatostatin receptors have been demonstrated with octreotide scintigraphy, somatostatin analogue octreotide treatment decreases hypophosphatemia and phosphate deficiency and that phosphate metabolism may be regulated by somatostatin receptors (Seufert et al., 2001). However, it was also observed that, Octreotide treatment does not yield the same results in all cases (Paglia F et al., 2002). Likewise, in the present case refractory to treatment, in controls made at 3, 6 ve 9th months after octreotide treatment, it was determined that dramatic improvement was seen in pain but without any biochemical changes. As previously reported for neuroendocrine tumors, heterogenous distribution of somatostatin receptors between tumor cells and hence higher number of cells lacking somatostatin receptors may have influenced treatment results (Wynick D et al., 1989). However, in a meta analysis has shown that the efficacy of somatostatin analogue octreotide treatment for preventing carcinoid crisis remains controversial (Guo and Tang, 2014).

Whether Octreotide treatment is actually effective in these tumors is still uncertain. In view of the heterogeneity of somatostatin receptors in PMT tumors, subgroups in which somatostatin receptors are more effective should be determined in order that unnecessary treatment attempts are avoided. In these rare tumors, multicenter studies may help to investigate the role of somatostatin analogs in treatment.

In conclusion, as these tumors are heterogeneous ones, in cases with positive gallium-68 and Octreotide scintigraphy, somatostatin treatment may exert positive effects on symptoms although radiological and biochemical benefit is not obtained.

References

- Carpenter TO (2003). Oncogenic osteomalacia - a complex dance of factors. *N Engl J Med*, **348**, 1705-8.
- Clifton-Bligh RJ, Hofman MS, Duncan E (2013). Improving diagnosis of tumor-induced osteomalacia with Gallium-68 DOTATATE PET/CT. *J Clin Endocrinol Metab*, **98**, 687-94.
- Folpe AL, Fanburg-Smith JC, Billings SD, et al (2004). Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol*, **28**, 1-30.
- Guo LJ, Tang CW (2014). Somatostatin analogues do not prevent carcinoid crisis. *Asian Pac J Cancer Prev*, **15**, 6679-83
- Houang M, Clarkson A, Sioson L, et al (2013). Phosphaturic mesenchymal tumors show positive staining for somatostatin receptor 2A (SSTR2A). *Hum Pathol Dec*, **44**, 2711-8.
- Jan de Beur SM, Streeten EA, Civelek AC (2002). Localisation of mesenchymal tumours by somatostatin receptor imaging. *Lancet*, **359**, 761-3.
- Jan de Beur SM (2005). Tumor-induced osteomalacia. *JAMA*, **294**, 1260-7
- Jonsson KB, Zahradnik R, Larsson T, et al (2003). Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med*, **348**, 1656-63.
- Paglia F, Dionisi S, Minisola S (2002). Octreotide for Tumor-Induced Osteomalacia *N Engl J Med*, **30**, 1748-9
- Reubi JC, Waser B, Laissue JA, Gebbers JO (1996). Somatostatin and vasoactive intestinal peptide receptors in human mesenchymal tumors: in vitro identification. *Cancer Res*, **56**, 1922-31
- Rodrigues NR, Calich AL, Etchebehere M, et al (2014). Whole-Body 99mTc-Octreotide Scintigraphy with SPECT/CT to Detect Occult Tumor Inducing Paraneoplastic Osteomalacia. *Clin Nuc Med*, **22**.
- Seufert J, Ebert K, Müller J et al (2001). Octreotide for tumor-induced osteomalacia. *N Engl J Med*, **345**, 1883
- Weider N, Santa Cruz D (1987). Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. *Cancer*, **59**, 1442-54.
- Wynick D, Anderson JV, Williams SJ, et al (1989). Resistance to metastatic pancreatic endocrine tumours after long-term treatment with the somatostatin analogue octreotide (SMS 201-995). *Clin Endocrinol*, **30**, 385-8.

**Arife Ulas¹, Didem Sener Dede²,
Mehmet Ali Nahit Sendur², Muhammed
Bulent Akinci², Bulent Yalcin²**

¹Ankara Ataturk Training and Research Hospital, ²Yildirim Beyazıt University, Faculty of Medicine, Ataturk Research And Training Hospital, Department of Medical Oncology, Ankara, Turkey *For correspondence: drarifeulas@hotmail.com