Dr Siva Sivapriyan
Dr Jesse Kumar
Dr Supriya Joshi
Dr Viktoriya Clarke

Maidstone and Tunbridge Wells NHS
NHS Trust

CASE: Thyroid dysfunction caused by three different Tyrosine Kinase inhibitors (TKI)

Introduction:

Tyrosine kinase inhibitors (TKIs) drugs used for the treatment of metastatic cancers including Renal cell carcinoma (RCC), gastrointestinal stromal tumours, thyroid and neuroendocrine tumours.

TKIs block vascular endothelial growth factor (VEGFR) and other growth factors (for example BCR-ABL).

Thyroid dysfunction is often a side effect of this treatment.

A close monitoring of thyroid hormone levels is a necessity.

Case:
69-year-old lady with RCC diagnosed in 2001.
Treated with three different types of TKIs:
Sunitinib (2010-12), Pazopanib (2012-16) & Axitinib (2016).
Diagnosed with Hypothyroidism in 2010, started on replacement.
At the beginning 2016 she developed profound clinical and biochemical hypothyroidism after initiation of Axitinib.
Her symptoms included tiredness and hair thinning and body aches.
Picked up by the biochemistry department and then Endocrinologists, who discussed case on MDT.
Communicated to the oncologists to increase thyroxine dose.

Date	TSH	FT4
26/11/15	4.5	24.3
21/01/16	4.7	23.7
18/02/16	11.4	19.1
01/03/16	21.0	17.1
17/03/16	26.0	15.0
14/04/16	24.4	17.6

Conclusion:

There is lack of awareness among clinicians about the significance of thyroid dysfunction related to TKI despite this being common.

Also we could prove different degrees of thyroid dysfunction with different TKIs in the same patient, Axitinib being the potent agent followed by Sunitinib and Pazopanib.

The research evidence in this area is scarce and there are no National guidelines about how to treat this.

Also a MDT approach is required as in this case to improve the patient outcome.

Discussion:

Multiple orally active tyrosine kinase inhibitors (TKIs) that blocks VEGF (vascular endothelial growth factor) and other growth factors (platelet-derived GF) are used to treat metastatic clear cell kidney carcinoma, gastrointestinal stromal tumours, thyroid carcinoma and pancreatic neuroendocrine tumours during the progression of the disease.

They have several side effects including cardiovascular effects (hypertension, left ventricular failure) and non-cardiovascular effects: proteinuria, bleeding, delayed wound healing, gastrointestinal perforation, fatigue, and dysphonia. Their additional side effects are gastrointestinal events (diarrhea, nausea), thyroid dysfunction, fatigue, stomatitis, myelosuppression, and cutaneous effects (including hand-foot syndrome), etc.
Sunitinib is one of earlier TKI and well know cause of thyroid dysfunction, typically hypothyroidism (1-3). Pazopanib appears to have the lowest reported incidence of thyroid complications, with <10 % of patients developing hypothyroidism in a phase III trial (5).
Axitinib is a newer agent. Early reports suggest a very high incidence and in a phase I trial, 89 % of patients had elevations in TSH (4).

Management

Because of the high prevalence of hypothyroidism, regular surveillance of TSH levels is warranted during therapy with antiangiogenic TKIs. We suggest that thyroid function be evaluated at baseline and monitored every 4 to 12 weeks thereafter and earlier if dictated by symptoms.
Thyroid hormone supplementation should be given to symptomatic patients with hypothyroidism.
In patients with subclinical hypothyroidism we are suggesting to take similar approach highlighted in the UK Guidelines for the Use of Thyroid Function Tests, July 2006 (6). It has highlighted that decision on treatment of patients with subclinical hypothyroidism should be guided by repeated TSH measurements. In patients with TSH >10 mU/L there is increasing evidence of progression to overt hypothyroidism and deterioration in hyperlipidaemia with the passage of time.There is evidence of improvement in the lipid profile and symptoms when patients with modestly raised TSH (mean 11.7mU/L) were rendered euthyroid with thyroxine.

1. Rini BI, Tamaskar I, Shaheen P, Salas R, Garcia J, Wood L, Reddy S, Dreicer R, Bukowski RM. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst. 2007;99(1):81.
2. Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH, Morgan JA, Dychter SS, Larsen PR, Demetri GD, Alexander EK. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med. 2006;145(9):660.
3. Feldt S, Schüssel K, Quinzler R, Franzmann A, Czeche S, Ludwig WD, Schulz M. Incidence of thyroid hormone therapy in patients treated with sunitinib or sorafenib: a cohort study. Eur J Cancer. 2012 May;48(7):974-81. Epub 2012 Feb 28.
4. Fujiwara Y, Kiyota N, Chayahara N, Suzuki A, Umeyama Y, Mukohara T, Minami H. Management of axitinib (AG-013736)-induced fatigue and thyroid dysfunction, and predictive biomarkers of axitinib exposure: results from phase I studies in Japanese patients. Invest New Drugs. 2012 Jun;30(3):1055-64. Epub 2011 Feb 8.
5. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, ZarbáJJ, Chen M, McCann L, Pandite L, Roychowdhury DF, Hawkins RE. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061

BES2016 90--EP
Thyroid
Siva sivappriyan
DOI: 10.3252/pso.eu.BES2016.2016
Poster presented at: SfE BES 2016 7-9 November BRIGHTON