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Hypothyroidism during treatment with tyrosine kinase inhibitors

Niedoczynność tarczycy w przebiegu leczenia inhibitorami kinaz tyrozynowych

Aneta L. Zygulska[1], Krzysztof Krzemieniecki[1], Anna Sowa-Staszczak[2]

[1]*Oncological Department, University Hospital, Krakow, Poland*
[2]*Endocrinological Department, University Hospital, Krakow, Poland*

Abstract

Tyrosine kinase inhibitors are relatively new targeted therapy drugs used for the treatment of metastatic clear cell kidney carcinoma, gastrointestinal stromal tumours, thyroid carcinoma and pancreatic neuroendocrine tumours during the progression of the disease. Hypothyroidism or thyroid dysfunction is often a side effect of this treatment. Therefore, monitoring of thyroid hormone levels before the beginning and during the treatment of tyrosine kinase inhibitors is a necessity. Hypothyroidism correlates with objective response to the treatment.
Sunitinib. This is the most described tyrosine kinase inhibitor which causes hypothyroidism. The mechanism of hypothyroidism is still unclear.
Sorafenib. Symptoms of hypothyroidism occur in 18% of patients treated with sorafenib due to metastatic renal cell carcinoma.
Imatinib. Hypothyroidism is one of the most frequent side effects of the treatment. Emergent tracheotomy was necessary due to larynx swelling during marked hypothyroidism.
Motesanib. Hypothyroidism or increased TSH level is diagnosed in 22% to 69% of patients with metastatic differentiated or medullary thyroid carcinomas. The management of patients with thyroid dysfunction and related symptoms such as fatigue is undoubtedly a challenge to an oncologist. **(Endokrynol Pol 2012; 63 (4): 302–306)**

Key words: *hypothyroidism, tyrosine kinase inhibitors*

Streszczenie

Inhibitory kinaz tyrozynowych są stosunkowo nowymi lekami z grupy przeznaczonej do terapii celowanych, stosowanymi w leczeniu nowotworów złośliwych, takich jak przerzutowy jasnokomórkowy rak nerki, stromalny nowotwór przewodu pokarmowego (GIST), raki tarczycy oporne na leczenie jodem radioaktywnym, przerzutowe guzy neuroendokrynne trzustki. Niedoczynność tarczycy lub dysfunkcja tarczycy są częstymi powikłaniami tego leczenia. Dlatego konieczne jest oznaczenie stężenia hormonów tarczycy przed rozpoczęciem i w trakcie leczenia inhibitorami kinaz tyrozynowych. Niedoczynność tarczycy pozostaje w ścisłym związku z obiektywną odpowiedzią na leczenie.
Sunitynib. Jest najczęściej opisywanym inhibitorem kinaz tyrozynowych, który wywołuje niedoczynność tarczycy. Mechanizm niedoczynności pozostaje niejasny.
Sorafenib. U 18% osób leczonych sorafenibem z powodu przerzutowego raka nerki występują objawy niedoczynności tarczycy.
Imatynib. Niedoczynność tarczycy jest jednym z najczęstszych powikłań leczenia imatinibem. W przebiegu nasilonej niedoczynności występowała konieczność wykonania pilnej tracheotomii z powodu obrzęku krtani.
Motesanib. Niedoczynność tarczycy lub podwyższone stężenie TSH jest rozpoznawane u 22–69% chorych na przerzutowego zróżnicowanego lub rdzeniastego raka tarczycy.
Postępowanie z chorymi z dysfunkcją tarczycy i ze współistniejącymi objawami, takimi jak zmęczenie, jest niewątpliwie wyzwaniem dla onkologa. **(Endokrynol Pol 2012; 63 (4): 302–306)**

Słowa kluczowe: *niedoczynność tarczycy, inhibitory kinazy tyrozynowej*

Introduction

Tyrosine kinase inhibitors are enzymatic receptor proteins which catalyse the transfer of phosphate from ATP to tyrosine present in the peptides. They are involved in the proliferation, angiogenesis, and invasiveness of the tumour. Tyrosine kinase inhibitors are the new multi-targeted therapy drugs used to treat haematological and solid tumours. They influence oncogenesis directly or indirectly through blocking tyrosine kinases. Tyrosine kinase inhibitors are not specific for one kind of tyrosine kinase, but most of them interact with vascular endothelial growth factor (VEGF), its receptor and platelet-derived growth factor receptors (PDGFR) [1].

Although they have the same mechanism of action, they differ from each other in the spectrum of targeted kinases, their pharmacokinetics, as well as specific adverse effects [2]. Erlotinib and gefitinib give the main spectrum of adverse events on skin and hair [2]. The

Aneta L. Zygulska MD, PhD, Oncological Department, University Hospital, ul. Śniadeckich 10, 31–531 Krakow, Poland, fax: +48 12 424 89 10, tel: +48 12 424 88 88, e-mail: zygulska@poczta.onet.pl

Table I. *Treatment of tyrosine kinase inhibitors and hypothyroidism (according to [1])*
Table I. *Leczenie inhibitorami kinazy tyrozynowej a niedoczynność tarczycy (wg [1])*

Author, year of publication	Drug	Number of subjects	Indication	Hypothyroidism [%]
Desai, 2006	Sunitinib	42	GIST	36
Mannavola, 2007	Sunitinib	24	GIST	71
Rini, 2007	Sunitinib	66	Renal cell carcinoma	85
Wong, 2007	Sunitinib	40	Solid tumours (mainly GIST)	53
Wolter, 2008	Sunitinib	59	Renal cell carcinoma/GIST	61
Schmidinger, 2011	Sunitinib/sorafenib	87	Renal cell carcinoma	36
Tamaskar, 2007	Sorafenib	39	Renal cell carcinoma	18
de Groot, 2005	Imatinib	11	Medullary thyroid carcinoma/ /GIST	100 in athyreotic subjects
de Groot, 2007	Imatinib	15	Medullary thyroid carcinoma	100 in athyreotic subjects
Sherman, 2008	Motesanib	93	Differentiated thyroid cancer	22
Schlumberger, 2009	Motesanib	91	Medullary thyroid carcinoma	29

commonest side effects associated with dasatinib and nilotinib are haematologic and cardiological [3].

Primary hypothyroidism is a rare complication of oncological treatment. Mainly interferon alpha and interleukin 2 cause hypothyroidism. Tyrosine kinase inhibitors often cause this side effect.

The first report on interaction between these drugs and thyroid function was published in 2005. Many papers have been published on this subject to date. The most important publications devoted to hypothyroidism as a result of treatment with tyrosine kinase inhibitors are set out in Table I [1].

The influence of the four multi-targeted therapy drugs i.e: sunitinib, sorafenib, imatinib, and motesanib on thyroid function are presented in this article.

Sunitinib

Sunitinib is an oral multi-targeted vascular endothelial growth factor and receptor tyrosine kinase inhibitor used for metastatic renal cell cancer and imatinib-resistant gastrointestinal stromal tumours, and recently in pancreatic neuroendocrine tumours (PNT) during the progression of the disease [4–6]. It is administered in a dose of 50 mg daily for four weeks, and the next two weeks of withdrawal, in PNT in a dose of 37.5 mg daily.

Retrospective studies indicate that sunitinib induces hypothyroidism in 53% to 85% of patients and prospective studies show that hypothyroidism is induced by sunitinib in 36% to 46% of patients [7–11]. The onset of hypothyroidism is unpredictable because significant differences in gender, age and severity of neoplastic disease are not observed. In general, hypothyroidism shows progressive worsening. Only in some cases is a sudden development of severe hypothyroidism diagnosed [8]. Hypothyroidism is revealed either in the first or second week of sunitinib therapy. Several authors have also found that TSH levels were elevated at the end of ON periods (four-week daily administration) and normalised at the end of OFF periods (two-week withdrawal), leading to intermittent hypothyroidism. After several treatment cycles, the baseline TSH levels seemed to increase, revealing a permanent hypothyroidism [1, 8]. Increased TSH (thyroid-stimulating hormone) level and decreased T3 (triiodothyronine) level are observed. Decreased T4 (tetraiodothyronine) level and free tyroxine index are seldom observed [9]. In general, thyroid impairment is diagnosed after two cycles of treatment [9]. According to Wong et al., hypothyroidism occurs on average after five months of therapy [10]. The mean time of onset of hypothyroidism after initiation for sunitinib therapy ranges from 12 to 50 weeks [11]. The risk of development of hypothyroidism increases with increasing duration of sunitinib therapy [11]. Symptoms of hypothyroidism such as: fatigue, cold intolerance, fluid retention, anorexia, skin and hair changes can be found in about 84% of patients with thyroid dysfunction [9]. Approximately 50% of those treated with sunitinib require supplementation of thyroid hormones, and levothyroxine reduced symptoms in 50% of treated patients [1, 10]. Because of this, routine monitoring of thyroid hormones is warranted before beginning, and every 2–3 months during, treatment with sunitinib [8–10, 12–15]. There is disagreement on the subject of the frequency of thyrotoxicosis caused by sunitinib.

According to some authors, thyrotoxicosis rarely occurs [16]. According to other sources, thyrotoxicosis is frequently diagnosed, which could be related to frequent monitoring of thyroid hormone level during treatment [13]. Sakurai presented sunitinib-induced thyrotoxicosis and destructive thyroiditis. Destructive thyroiditis is diagnosed based on increased thyroglobulin level, a low radioactive uptake, increased free thyroxine level, and suppressed TSH level. It is characterised by transient thyrotoxicosis with complete recovery. Sometimes it is followed by transient and persistent hypothyroidism [17]. An algorithm to diagnose and treat thyroid dysfunction during sunitinib treatment is presented in Figure 1 [16].

The pathophysiologic mechanism of hypothyroidism induced by sunitinib is still unclear [4, 13]. Different mechanisms have been considered in order to explain this hypothyroidism.

The influence of progressive depletion of functional reserves, selected inhibition iodine thyroidal uptake, direct effect on sodium iodide symporter (NIS) or TSH receptor or thyroid atrophy as a result of blocking the gland vascularisation has been investigated [9]. Decreasing blood flow in vessels as a result of VEGFR blocking decreases shrinkage of thyroid gland dimensions [18–20].

After definitive completion of sunitinib, TSH level returns in the normal range after a maximum period of 60 days. This suggests that hypothyroidism is transitory and it shows that blocking of iodine uptake is directly related to the drug administration, similarly to the other side effects of the drug [8]. On the other hand, a study on rat thyroid cells excluded the possibility of iodine uptake inhibition [4].

Sunitinib inhibits thyroid peroxidase activity decreasing thyroid hormones synthesis, and in this way sunitinib contributes to hypothyroidism [10].

Individual cases of lymphocytic thyroiditis during sunitinib treatment have been described, suggesting that sunitinib could trigger an autoimmunological process in the thyroid gland [16, 21]. However, the direct toxic influence of thyroid cells and autoimmunological background have been excluded [8]. There is a lack of cytological evidence for the presence of thyroid tissue inflammation changes, and on this basis, a hypothesis has been put forward that hypothyroidism is caused by sunitinib-induced follicular cell apoptosis [7].

Hypothyroidism during sunitinib treatment of patients with metastatic renal cell cancer can correlate with objective response to this therapy [22].

Hypothyroidism can be considered as a marker of response to treatment with this drug.

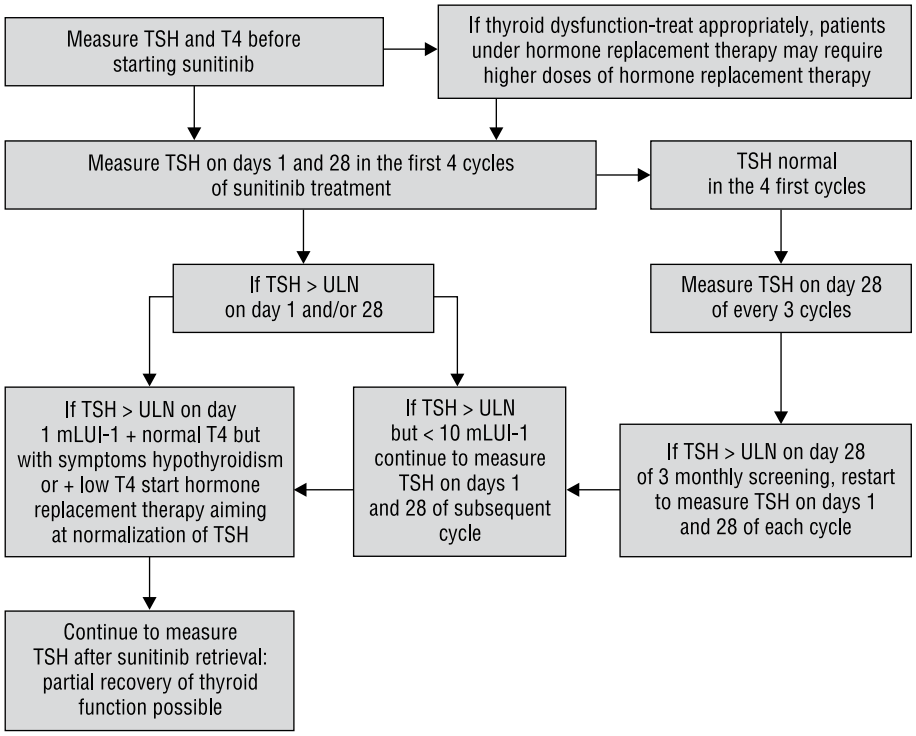

Figure 1. *Algorithm to diagnose and treat thyroid dysfunction during sunitinib (according to [16]); TSH — thyroid-stimulating hormone; T4 — tetraiodothyronine; UNL — upper limit of normal*

Rycina 1. *Algorytm diagnozowania i leczenia dysfunkcji tarczycy podczas leczenia sunitynibem (wg [16]); TSH — hormon tyreotropowy; T4 — tetrajodotyronina; UNL — górna granica normy*

Sorafenib

Sorafenib is an oral multi kinase inhibitor such as: raf, VEGFR1, VEGFR2, VEGFR3, protein c-Kit, PDGFR beta, RET, fms. It is approved for metastatic renal cell carcinoma and unresectable hepatocellular carcinoma [1, 23]. Sorafenib is effective both in metastatic and locally advanced medullary thyroid carcinoma and nonmedullary thyroid carcinoma [24]. The administration of sorafenib is 800 mg daily. One cycle lasts four weeks. Hypothyroidism is one of the side effects of sorafenib, but it does not occur as frequently as with sunitinib [22, 23]. Hypothyroidism can persist after completion of sorafenib treatment [1]. Sorafenib is associated with increased TSH levels in 33% of thyroid carcinoma patients [25]. Biochemical features of hypothyroidism occur in 18% of those treated with sorafenib due to metastatic clear cell renal carcinoma [23, 26]. Dysfunction of thyroid is usually of short duration and it seldom requires supplementation [22]. Subclinical hypothyroidism is related to the rate of objective response. This indicates that hypothyroidism can serve as a marker of response to therapy with sorafenib due to metastatic renal cell carcinoma [22]. Abdulrahman hypothesised that sorafenib may influence the activities of iodothyronine deiodinases (D1, D2 and D3). It probably causes enhanced T4 and T3 metabolism and may contribute to hypothyroidism during sorafenib therapy [24].

Imatinib

Imatinib is an oral tyrosine kinases inhibitor such as: Bcr-Abl, PDGFR alpha, PDGFR, c-Fms, c-Kit [1, 14]. Imatinib is approved for chronic myeloid leukemia, metastatic gastrointestinal stromal tumours and dermatofibrosarcoma [1, 14, 27]. The efficacy of imatinib has been investigated in medullary thyroid cancer. There was no objective response, but toxicity was significant. Hypothyroidism in G3 degree was the commonest side effect. It occurred in 33% of patients treated with imatinib [14].

Hypothyroidism is reversible through increasing doses of hormones thyroid supplementation [28]. In a few patients with significant hypothyroidism, there occurred swelling of the larynx which required emergent tracheotomy [14]. Patients with hypothyroidism who are taking imatinib should have the exact increasing level of thyreotropins monitored. It indicates marked hypothyroidism and requires escalation of hormone thyroid dosage [28].

Dora et al. did not prove the effect of imatinib on thyroid dysfunction. There was no correlation between TSH level and dose, duration of treatment or the cumulative dose of imatinib [27]. But these results should be interpreted with great caution because of the small number of patients enrolled in the trial; even a correlation between imatinib treatment and dysfunction of thyroid has not been confirmed so far.

Motesanib (AMG 706)

Motesanib is an oral tyrosine kinase inhibitor such as: VEGR r1 VEGR r2, VEGR r3, PDGFR, RET, KIT [1, 29, 30]. Clinical trials have been conducted related to the efficacy of motesanib in radioiodine-resistant differentiated thyroid carcinoma, medullary thyroid carcinoma and other solid tumours [1, 29–31]. The action of motesanib can be doubled through its influence on both thyroid tissue and thyroid hormones [1]. In a two-phase trial among patients with metastatic or advanced differentiated or medullary thyroid carcinoma treated with motesanib, hypothyroidism occurred in 22% of patients with differentiated thyroid carcinoma and in 29% to 61% of patients with medullary thyroid carcinoma [30, 31]. Therefore the dose of levotyroxine required escalation [1].

It appears that motesanib is a new achievement in the treatment of differentiated and medullary thyroid carcinomas.

Conclusions

Hypothyroidism is a frequent side effect of tyrosine kinase inhibitors treatment.

A thyroid function test assessment is necessary before beginning and during therapy with tyrosine kinase inhibitors.

Thyroid hormone replacement therapy should be considered in the case of clinical explicit hypothyrodism.

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