Tyrosine kinase inhibitors and hypothyroidism - an intriguing link

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Abstract
Purpose: Along with increased cancer incidence, there is also an increased use of targeted cancer therapy. One of the most potent classes of targeted therapy drugs are tyrosine kinase inhibitors (TKIs). Several new TKIs have become available in clinical practice after the correlation of sunitinib and hypothyroidism was documented. The aim of this review is to assess all relevant studies regarding clinically approved TKIs, in respect to hypothyroidism as a side-effect, and to investigate the possible predictive value of hypothyroidism in patients taking these drugs.

Methods: Drugs that are approved by the United States Food and Drug Administration (FDA) for clinical use are evaluated in this study. In order to identify studies regarding hypothyroidism as a side-effect of TKIs, a systematic PubMed/Medline literature search was conducted.

Results: Currently, the FDA has approved 26 different TKIs for use in clinical practice. The total number of yielded PubMed/Medline results was 232.

Conclusions: Sunitinib, sorafenib, imatinib, pazopanib, and axitinib are TKIs with a definitive link to hypothyroidism. According to some current studies, patients who develop hypothyroidism during TKI therapy have prolonged progression-free survival. Despite the fact that hypothyroidism is nowadays a well known side-effect of therapy with many different TKIs, there are still no established guidelines for its treatment. Further studies in this area are needed, especially for lesser investigated drugs. It would be prudent to consider routine monitoring of thyroid function in all patients who receive TKIs, and to recommend endocrinological consultation as necessary.

Key words: tyrosine kinase inhibitors; hypothyroidism; side effects; cancer.
1. Introduction

The global incidence of cancer is continually rising, with more than 14,068,000 new cases and 8,202,000 deaths in 2012, making it the second most common cause of death in developed regions after cardiovascular disease [1]. Along with increased incidence, there is also an increased use of targeted cancer therapy, designed to interfere with specific molecules necessary for tumor growth and progression, in contrast to chemotherapy, which is rather unselective. This therapy, due to the proposed mechanism of action, should be more precise with fewer side-effects. Although this has been proved in clinical practice, these drugs exhibit a distinct pattern of side-effects that require appropriate monitoring and management [2].

One of the most potent classes of targeted therapy drugs are tyrosine kinase inhibitors (TKIs), used in many different cancer types. Tyrosine kinases, a subclass of protein kinases, are enzymes that transfer a phosphate group from adenosine triphosphate to a protein in a cell. They play a critical role in the modulation of growth factor signaling, since activated forms of these enzymes can increase tumor cell proliferation and growth, induce apoptotic affects, and promote angiogenesis and metastasis. TKIs inhibit these enzymes, thus disabling a downstream signal transduction into the cell. Since tyrosine kinases are not only present on cancer cells, but are widespread in the body, TKIs may exhibit several side-effects many of which are common to this class of drugs. However, due to various mechanisms used to achieve selectivity, and the difference in number of potential targets (multi- vs. single-targeted), some of the observed side-effects are specific to certain TKIs.

Hypothyroidism is one of the common side-effects of TKIs, which is known to be correlated with several of these drugs, occurring at various rates, depending on the specific drug used [3]. The varying occurrence rate is probably due to different mechanisms of action of specific drugs, making some of them more, and others less potent in the sense of causing hypothyroidism. Although some other thyroid disorders may occur, such as thyrotoxicosis, they are usually transient and less common [4]. Although the clinical course is usually mild, unrecognized hypothyroidism can have severe, and even fatal consequences in some patients [5]. Additionally, the importance of TKI-induced hypothyroidism increased when several authors proposed that some side-effects, such as hypertension, hypothyroidism and hand-foot syndrome may serve as potential predictive biomarkers of treatment efficacy in one of the most commonly used TKI, sunitinib [6-9]. Thus, optimal and timely diagnosis, follow-up during TKI therapy, as well as treatment of hypothyroidism is highly significant. Since several new drugs have become available in clinical practice after the correlation of sunitinib and hypothyroidism was documented, the aim of this review is to assess all relevant studies regarding clinically approved TKIs, in respect to hypothyroidism as a side-effect, and to investigate the possible predictive value of hypothyroidism in patients taking these drugs.

2. Materials and Methods

Since a large number of TKIs are currently under investigation for possible antitumor effects in various malignancies, we included those that are approved by the United States Food and Drug Administration (FDA) for clinical use [10]. In order to identify studies evaluating hypothyroidism as a side-effect of tyrosine kinase inhibitors, a systematic PubMed/Medline literature search was conducted. The search terms used included “hypothyroidism” in combination with generic names of all TKIs that were investigated in this study (e.g. “hypothyroidism AND afatinib”). In addition, the references of selected articles were checked in order to identify papers not detected by our search strategy. All available papers were evaluated and the link between newer TKIs and hypothyroidism was assessed. Papers that evaluated more than one TKI were added to the total number of publications for each drug. Also, drug safety information was assessed, in order to check for possible inclusion of hypothyroidism in the list of known side-effects. The cut-off date for the study search was the 9th December 2015. Our search strategy yielded 232 potentially relevant citations for 26 currently FDA-approved TKIs from PubMed/Medline.

For 5 of the drugs that are already known to cause thyroid dysfunction in a significant proportion of patients (axitinib, imatinib, pazopanib, sorafenib, sunitinib), for final analysis only full-length publications in English
were included. Review articles, as well as case reports and other short-length publications, such as letters to the editor, were excluded. Additionally, theoretical studies that did not include any patients were excluded. At least two authors independently selected articles for inclusion criteria.

3. Results

Currently, 26 different TKIs have been approval by the FDA for use in clinical practice. The total number of PubMed/Medline results when a search including the generic drug name and term “hypothyroidism” was conducted is shown in Table 1, and association between different TKIs with hypothyroidism is presented in Table 2. For 11 TKIs, no studies linking these drug to hypothyroidism were found, and after checking drug safety information a potential link with thyroid disorders was only found for lenvatinib, which may cause changes in thyroid hormone levels. For the other 10 drugs, safety information did not mention any possible thyroid disorders. Table 3 presents more detailed information on 5 drugs with a definitive and known link to hypothyroidism.

4. Discussion

4.1. TKIs with a confirmed link to hypothyroidism

Axitinib is a small molecule TKI. It is an inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, VEGFR2, VEGFR3, mast/stem cell growth factor receptor (c-Kit), and platelet-derived growth factor receptor (PDGFR), thus consequently inhibiting angiogenesis. It is approved for the treatment of patients with renal cell carcinoma (RCC). Results of the phase III trial AXIS have shown that 20% of patients on axitinib were found hypothyroid, and 27% either started therapy with or increased their thyroid hormone dose. In this study, hypothyroidism was found to be more commonly associated with axitinib than with sorafenib (21% vs. 7%) [11]. In a subgroup analysis of Japanese patients, the observed difference was even larger (44 vs. 24%) [12]. The diagnosis of hypothyroidism in either arm was more common among Japanese than in the overall population, although the incidence of thyroid-stimulating

<table>
<thead>
<tr>
<th>Tyrosine kinase inhibitor</th>
<th>PubMed results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>117</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>48</td>
</tr>
<tr>
<td>imatinib</td>
<td>24</td>
</tr>
<tr>
<td>pazopanib</td>
<td>13</td>
</tr>
<tr>
<td>axitinib</td>
<td>11</td>
</tr>
<tr>
<td>dasatinib; nilotinib; regorafenib; vandetanib</td>
<td>3</td>
</tr>
<tr>
<td>erlotinib</td>
<td>2</td>
</tr>
<tr>
<td>cabozantinib; gefitinib; lapatinib; nintedanib; tivozanib;</td>
<td>1</td>
</tr>
<tr>
<td>afatinib; bosutinib; ceritinib; crizotinib; ibrutinib; lenvatinib; pegaptanib; ponatinib; ruxolitinib; tofacitinib; trametinib</td>
<td>0</td>
</tr>
</tbody>
</table>

* per each drug
hormone (TSH) elevation ≥ 10 μIU/ml among patients who had TSH < 5 μIU/ml before treatment was comparable between Japanese patients and the overall population [12]. In phase II and phase I trials, incidence of hypothyroidism was even higher, up to 89% of patients experienced elevation of TSH above the upper limit of normal range [13,14].

Imatinib is a 2-phenyl amino pyrimidine derivate, inhibiting a number of tyrosine kinase enzymes. It occupies tyrosine kinase domain in Ableson proto-oncogene, c-Kit and PDGFR. It is approved for treatment of patients with Philadelphia-positive (Ph+) chronic myelogenous leukemia (CML), relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL), gastrointestinal stromal tumors, dermatofibrosarcoma protuberans, as well as some other less common cancer types. In a study of 15 patients with metastatic medullary thyroid carcinoma (MTC), de Groot et al. concluded that patients receiving imatinib have a high likelihood for increased levothyroxine replacement, and risk of serious thyroid toxicity is especially high in initially hypothyroid patients. Similarly to sunitinib, hypothyroidism in patients who are treated with imatinib can be potentially fatal, since in 2 of these 15 patients larynx swelling during marked hypothyroidism was reported, requiring emergent tracheotomy [5,15].

Pazopanib is a selective multi-targeted TKI receptor, with c-Kit, fibroblast growth factor receptor (FGFR), PDGFR, and VEGFR being among the inhibited enzymes. It is approved for the treatment of RCC and soft tissue sarcoma. Matrana and associates evaluated outcomes of patients with metastatic clear cell RCC treated with pazopanib after progression during treatment with other targeted therapies. The rate of hypothyroidism in these patients was 18.2%, mostly grade 2, although a large proportion of these patients also received other TKIs (mostly sunitinib) before pazopanib, making it difficult to conclude which drug initially caused thyroid toxicity [17]. However, several other studies directly connected pazopanib to hypothyroidism, although rates were lower (≤12%) [18,19].

Sorafenib is a small molecular TKI, inhibiting VEGFR, PDGFR, and Raf kinases. It is used for the treatment of patients with metastatic RCC, advanced hepatocellular carcinoma, and radioactive iodine-resistant advanced thyroid cancer. There is a definitive link between hypothyroidism and sorafenib, as described in all conducted clinical trials and numerous case reports. The observed rate of thyroid toxicity is, however, different among studies, and ranges from 6.3% to 27% [11,12,20-22].

Decline in thyroid function is followed by a change in thyroid size. In a study on 42 RCC patients receiving sorafenib or sunitinib, thyroid was reduced in size to 89 ± 16% after 3 months of therapy, 81 ± 21% after 6 months, 71 ± 21% after 9 months and 68 ± 21% after 12 months in patients who developed hypothyroidism, whereas the patients without thyroid dysfunction maintained a thyroid size of 90 ± 12% even after 12 months [23]. Several authors also proposed that patients with RCC who develop hypothyroidism during sorafenib therapy have better outcomes, in terms of longer progression-free survival (PFS) [24].

Sunitinib is an oral, small molecule, multi-targeted TKI, inhibiting all PDGFRs, all VEGFRs, and CD117. It is approved for the treatment of RCC, and gastrointestinal stromal tumors (GISTs) resistant to therapy with imatinib. Hypothyroidism is one of the most common side-effect of sunitinib therapy, along with hypertension, hand-foot syndrome, diarrhea, fatigue, and stomatitis [25]. The majority of studies (mostly regarding RCC), have found that the rate of hypothyroidism varies significantly among different patient groups, and occurs in 14 to 70% of patients treated with sunitinib, making it a very common side-effect [26-29]. Additionally, in some of these studies, thyroid function assessment was not done on a regular basis, thus the true incidence could be even higher. Although common, sunitinib-induced hypothyroidism is usually mild, and can be easily treated with thyroid hormone replacement therapy. Recently, several papers have discussed hypothyroidism as a potential predictive marker of better treatment response with sunitinib, and concluded that the occurrence of hypothyroidism prolongs PFS or even overall survival (OS), although some authors did not confirm these hypotheses [28,30-33].
### Table 2. Association of TKIs and hypothyroidism

<table>
<thead>
<tr>
<th>Tyrosine kinase inhibitor</th>
<th>Hypothyroidism rate</th>
<th>Link to hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>axitinib</td>
<td>19 – 89%</td>
<td>definite</td>
</tr>
<tr>
<td>cabozantinib</td>
<td>78.7%</td>
<td>probable</td>
</tr>
<tr>
<td>dasatinib</td>
<td>50%</td>
<td>possible, but still questionable</td>
</tr>
<tr>
<td>erlotinib</td>
<td>unknown</td>
<td>possible, but still questionable</td>
</tr>
<tr>
<td>gefitinib</td>
<td>unknown</td>
<td>possible, but still questionable</td>
</tr>
<tr>
<td>imatinib</td>
<td>13%</td>
<td>definite</td>
</tr>
<tr>
<td>lapatinib</td>
<td>unknown</td>
<td>unprobable</td>
</tr>
<tr>
<td>nilotinib</td>
<td>22%</td>
<td>probable</td>
</tr>
<tr>
<td>nintedanib</td>
<td>3.1%</td>
<td>possible, but still questionable</td>
</tr>
<tr>
<td>pazopanib</td>
<td>7 – 18.2%</td>
<td>definite</td>
</tr>
<tr>
<td>regorafenib</td>
<td>1.5 – 41.7%</td>
<td>very probable</td>
</tr>
<tr>
<td>sorafenib</td>
<td>6.3 – 27%</td>
<td>definite</td>
</tr>
<tr>
<td>sunitinib</td>
<td>14 – 70%</td>
<td>definite</td>
</tr>
<tr>
<td>tivozanib</td>
<td>unknown</td>
<td>possible, but still questionable</td>
</tr>
<tr>
<td>vandetanib</td>
<td>84.6%</td>
<td>possible, but still questionable</td>
</tr>
</tbody>
</table>

### Table 3. Total number of publications, number of reviews, and total number of original articles with time frame and tumor type for five TKIs with the most definite link to hypothyroidism

<table>
<thead>
<tr>
<th>TKI</th>
<th>Tumor type</th>
<th>Publications in total</th>
<th>Original articles</th>
<th>Reviews</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>axitinib</td>
<td>RCC</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>2010 – 2015</td>
</tr>
<tr>
<td>imatinib</td>
<td>GIST, MTC, CML</td>
<td>24</td>
<td>9</td>
<td>10</td>
<td>2005 – 2014</td>
</tr>
<tr>
<td>pazopanib</td>
<td>RCC, STS</td>
<td>13</td>
<td>5</td>
<td>7</td>
<td>2010 – 2014</td>
</tr>
<tr>
<td>sorafenib</td>
<td>RCC; HCC</td>
<td>48</td>
<td>28</td>
<td>17</td>
<td>2007 – 2015</td>
</tr>
<tr>
<td>sunitinib</td>
<td>RCC, GIST</td>
<td>117</td>
<td>56</td>
<td>31</td>
<td>2006 – 2015</td>
</tr>
</tbody>
</table>

TKI, tyrosine kinase inhibitor; RCC, renal cell carcinoma; GIST, gastrointestinal stromal tumor; MTC, medullary thyroid carcinoma; CML, chronic myelogenous leukemia; STS, soft tissue sarcoma; HCC, hepatocellular carcinoma.
4.2. TKIs with limited evidence-link to hypothyroidism

For 10 drugs, there is still only limited evidence of causative association with hypothyroidism, since the total number of studies linking these TKIs to hypothyroidism is only 19, comprising 8.3% of all studies, while these drugs comprise 38.5% of all investigated TKIs. However, the strength of evidence varies among these drugs (Table 2). Cabozantinib, nilotinib and regorafenib are probably among those that may cause hypothyroidism in a significant proportion of patients. The rate of thyroid disorders in patients receiving cabozantinib was evaluated in only one study, which included patients from 2 clinical trials (NCT01688999 for metastatic bladder cancer, and NCT01755195 for metastatic soft tissue sarcoma); however, the rate of thyroid dysfunction was very high, occurring in 93.1% of patients [34]. Hypothyroidism itself occurred in 26 out of 33 included patients (78.7%). In one study, dasatinib and nilotinib also showed high rates of hypothyroidism, 50% and 22%, respectively; however, in the dasatinib group there were only 10 investigated patients (55 in the nilotinib group) [35]. The other 2 papers with dasatinib were reviews by Fallahi et al, and Hartmann et al, which evaluated a large number of TKIs together, thus making direct conclusions regarding individual drugs difficult [36,37]. On the other hand, nilotinib was also evaluated in one of these reviews, as well as one case report, with hypothyroidism occurring in a patient treated for CML [36,38]. Correlation of erlotinib and hypothyroidism was evaluated in one review and one case report, in a patient with preexisting subclinical hypothyroidism which developed before the start of erlotinib therapy, thus conclusions can not be clearly made [37,39]. Gefitinib and tivozanib were only investigated in 2 formerly mentioned reviews, thus no relevant data linking these drugs to hypothyroidism are available to date [36,37]. Laptatinib appeared in only one publication, which evaluated the relationship between TKIs and hypothyroidism, but without any conclusions, because the main first line drugs in this study were sunitinib and sorafenib, while laptatinib, as a second-line treatment was given to only one patient [40]. Thus, hypothyroidism as a side-effect of this drug is, according to currently available data, not probable. In a head-to-head study comparing sunitinib as first line therapy in metastatic RCC, nintedanib showed a lower incidence of high grade toxicities, including thyroid-related ones [41]. The reported rate of hypothyroidism was very low, 3.1% [41]. There are no other currently available studies with nintedanib, thus conclusions are still difficult to make. In contrast, although only 3 papers were found for regorafenib when a PubMed/Medline search was conducted, it is a drug with a clear link to hypothyroidism. It is included in one review with 7 other TKIs, but there are also 2 original articles with direct investigation of regorafenib in patients with colorectal and hepatocellular cancer [42-44]. The observed rate of hypothyroidism was high, up to 41.7% [44]. For vandetanib, a connection to hypothyroidism is possible, but still not definite. It is evaluated in 2 of the formerly mentioned reviews with a large number of included TKIs, and in only one original article on pediatric patients treated for MTC [36,42,45].

4.3. TKIs with no reported connection with hypothyroidism

According to the conducted PubMed/Medline search, no papers linking afatinib, bosutinib, ceritinib, crizotinib, ibrutinib, lenvatinib, pegaptanib, ponatinib, ruxolitinib, tofacitinib or trametinib to hypothyroidism as a side-effect of therapy were published, even in the form of an individual case report. This group represents 11 out of the 26 currently clinically approved TKIs by the FDA, or 42.3%, meaning that a large proportion of TKIs may not be linked to thyroid disorders in comparison to some other TKIs, especially older ones. The slight differences in their mechanism of action could explain the different toxicity profiles. Although all of these drugs work by inhibiting tyrosine kinases, their binding sites are heterogenous, which also enables them to be used in different tumor types. Also, it has been speculated that even the same drug could induce different side-effects when given to patients with different types of cancer. Sunitinib, as one of the most widely used TKIs, presented a
different ratio of the same side-effects in patients with GIST, than it was formerly registered in patients with metastatic RCC [46]. The underlying mechanisms behind this are still mostly unknown. However, since some of mentioned drugs are only recently approved for routine clinical use, data regarding their toxicity profile may still be incomplete. Thus, it is still possible that some patients using TKIs that are currently not known to be associated with hypothyroidism may develop thyroid disorders. Since it was shown that unrecognized and unregulated thyroid disorders might cause serious clinical complications, clinicians should keep this in mind when using TKIs, especially newer ones. Patients who use these drugs should clinically examined for possible thyroid-related symptoms, with thyroid hormone level evaluation in cases of clinical suspicion.

4.4. Thyroid dysfunction mechanisms

Although the definitive mechanism of TKI-induced hypothyroidism is still the subject of an ongoing debate, several theories have been proposed. However, it is still not known whether all of these mechanisms need to be active together in an individual patient, or hypothyroidism can be caused by multiple mechanisms, because contradictions among the currently available studies exist. As one of the most widely used TKIs, with hypothyroidism as a very common side-effect, sunitinib is a drug with the most available data.

According to current data, VEGF inhibition is among the most probable mechanisms of thyroid toxicity caused by sunitinib. VEGF is a signal protein that stimulates vasculogenesis and angiogenesis, allowing formation of new blood vessels after injury and exercise, as well as formation of collateral circulation. Through inhibition of VEGFR, sunitinib reduces blood flow to the tumor, as well as tumor angiogenesis, leading to tumor regression. However, along with this anti-tumor effect, capillary regression is observed in normal organs as well. Considering that the thyroid is an organ with the highest blood flow rate per unit weight, sunitinib-induced thyroid toxicity is a clear consequence of this mechanism [47].

In a combined prospective study on RCC or GIST patients and rats, Kappers and colleagues explained that alterations in thyroxine/triiodothyronine metabolism could also be among the causes of hypothyroidism. At week 10 of treatment, increased TSH levels were accompanied by a decreased triiodothyronine / reverse triiodothyronine ratio [48]. Induction of type 3 deiodinase activity was also proposed as a mechanism of thyroid toxicity in sorafenib as well, as presented in another prospective study on 21 patients with progressive nonmedullary thyroid carcinoma [49].

Another possible mechanism is blockage of radioactive iodine uptake, as proposed by Mannavola et al. The authors reported significant variations in I-123 uptake, and after exclusion of autoimmune and/or destructive mechanisms, concluded that impaired iodine uptake is the underlying mechanism. The observed incidence of hypothyroidism was high (46%), and although TSH levels normalized at the end of OFF periods (during pause of the drug), later worsening of thyroid function was documented, with several clinically severe cases [50]. New data show that autoimmunity could also be involved in the effect of sunitinib on the thyroid. In a recent study by Pani et al. on 27 patients with various metastatic carcinomas, it was shown that in 25% of patients anti-thyroid peroxidase antibodies (TPOAb) became detectable, and TPOAb-positive patients displayed a higher degree of hypothyroidism and thyroid volume reduction. This subgroup of patients also had significantly longer PFS, when compared to TPOAb-negative patients [51].

4.5. Association between hypothyroidism and survival

Recently, several authors have discussed the predictive value of hypothyroidism when TKIs are used, with most of these studies presenting patients who were taking sunitinib. The majority of papers
concluded that the occurrence of hypothyroidism is linked to prolonged PFS [28,30,31], and one study even reported longer OS and overall response rate (ORR) [32]. On the other hand, Sabatier et al. investigated the outcome of 111 patients taking sunitinib, and found no correlation between thyroid dysfunction and longer PFS nor OS. However, results were based on the assessment of thyroid function after 6 months of therapy, and no further data were reported (median PFS for the entire patient population was 11.7 months) (33). Although other TKIs are less investigated in this setting, there are also some data proposing hypothyroidism as a predictive marker in these drugs as well. Several authors concluded that the occurrence of hypothyroidism in patients taking sorafenib is also a marker of better treatment response, mainly in terms of prolonged PFS, while one study with axintinib concluded that TSH might act as a biomarker of plasma exposure of the drug [14,20,52]. In accordance with this data, the predictive value of hypothyroidism is currently investigated in several different TKIs, even in those that are not yet FDA-approved. For example, one study confirmed hypothyroidism as a biomarker of efficacy of famitinib in patients treated for metastatic breast cancer [53]. According to these findings, patients who develop hypothyroidism during TKI therapy have prolonged PFS, while there is probably no association with OS. However, since sunitinib and some other TKIs provoke thyroid toxicity, possible bias linked to the length of the therapy should also be considered. Considering that hypothyroidism may occur at any time during treatment, its incidence increases over time in patients who receive TKI therapy. Thus, subgroups of patients who have the longest survival also have the highest incidence of hypothyroidism, since there is enough time for thyroid toxicity to develop.

Additionally, one of the observed problems in clinical practice is that several TKIs are often used in sequential therapy (therapy with one TKI after therapy with another TKI), increasing the chance of cumulative toxicity. In a retrospective analysis of 5739 patients in nine trials, Porta et al. concluded that hypothyroidism is the only adverse effect with cumulative toxicity. In this study, the rate of hypothyroidism increased by interval analysis from 6% at 0–<6 months to 42% at 5–<6 years and by cumulative analysis from 14% at 0–1 years to 36% over 6 years [54]. Thus, in sequential therapy it is not always clear which of the TKIs in sequence caused thyroid toxicity, and determination of the hypothyroidism rate in the second and further lines of therapy may yield some false positive results, caused by drugs used in former lines.

4.6. Other types of iatrogenic hypothyroidism

Although there are published publications on the topic of TKI-induced hypothyroidism, data are still scarce. This can be explained by the fact that TKIs, although used in clinical practice for a number of years, are still relatively new drugs when compared to some other groups of medications for which hypothyroidism is described as a known side-effect. Some formerly described causes of iatrogenic hypothyroidism include drugs used for hyperthyroidism (such as propylthiouracil, radioactive iodine, potassium iodide, methimazole), lithium, amiodarone, nitroprusside, perchlorate, povidone iodide, and sulfonylureas. For comparison, PubMed/Medline search of terms “amiodarone AND hypothyroidism” yielded 489 results, much more than for all TKIs combined. Consequently, the mechanisms of thyroid dysfunction development are also explained more extensively in these “older” drugs.

5. Conclusion

Despite the fact that hypothyroidism is nowadays a well known side-effect of therapy with many different TKIs, there are still no definitely established guidelines. In most patients, sunitinib-induced hypothyroidism can be easily treated with thyroid hormone replacement therapy, but there is some uncertainty regarding which patients should be treated. According to most experts in the area, only patients with symptomatic hypothyroidism (grade 2 or higher) should receive levothyroxine [20]. Another question arises regarding different mechanisms of action, as well as different mechanisms of inducing thyroid toxicity. It is still not clear whether a general approach for the treatment of TKI-induced hypothyroidism should be followed, or some specific mechanisms and
target molecules of certain TKIs should be taken into account. Further studies in this area are needed to resolve these issues. It would be prudent to consider routine monitoring of thyroid function in all patients who receive TKIs, and especially those that are already known to cause thyroid toxicity, and to recommend endocrinological consultation as necessary.

Author contributions

DK performed literature review, wrote the article and gave the final approval. MP gave the idea for the article, participated in drafting the article and gave the final approval. IK, AB and ZK critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.

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