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Incidence of thyroid hormone therapy in patients treated with sunitinib or sorafenib: A cohort study

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Abstract Background: Sunitinib and sorafenib can induce serious adverse drug reactions (ADR) such as hypothyroidism. However, the incidence has not been reliably determined in clinical trials.

Aims: To determine incidence rates (IR) and hazard ratios (HR) of thyroid hormone (TH) therapy as a surrogate for sunitinib- and sorafenib-induced clinical hypothyroidism.

Methods: A cohort study was performed using claims data for prescriptions covering >80% of German pharmacies. Patients with a first prescription of sunitinib or sorafenib in the period between June 2006 and December 2007 were followed until incident prescription of any TH (event of interest) or censoring (due to loss to follow-up, discontinuation or switch of therapy, prescription of antithyroid drugs or the end of the study).

Results: One-hundred and seventy eight of 1295 sunitinib patients (13.7%) versus 77 of 1214 sorafenib patients (6.3%) received a TH. IR were 24.2 and 12.1 per 100 person-years, respectively. Unadjusted HR for TH therapy was 2.0 (95% confidence interval (CI) 1.5–2.6) for sunitinib compared to sorafenib and remained significant after adjustment for covariates, i.e. type of prescriber, region, insurance status, type of insurance fund, and relevant co-medication.

Conclusions: Sunitinib- and sorafenib-induced hypothyroidism is a more frequent ADR than currently labelled. Furthermore, patients treated with sunitinib have a two-fold increased risk of requiring TH therapy compared to sorafenib. Patients being treated with sunitinib or sorafenib are, therefore, at risk of thyroid function disturbances and routine monitoring both at baseline and throughout treatment with sunitinib and sorafenib is justified.

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1. Introduction

The multi-kinase inhibitors (MKI) sunitinib and sorafenib received approval for the treatment of metastatic and advanced renal cell carcinoma in 2006. Both substances block signal cascades that are activated by the vascular endothelial growth factor (VEGF).^{1,2}

From the therapeutic point of view, there has been a great need in developing new treatment options for advanced renal cell carcinoma for a long time as the previous standard treatment with unspecific interferon- α -2a has only a low response rate and is associated with severe adverse drug reactions (ADR).³

The efficacy has been proven in advanced and metastatic renal cell carcinoma pivotal trials for both sunitinib and sorafenib.^{4,5} Sunitinib has become standard therapy in first-line and sorafenib in second-line treatment of metastatic renal cell carcinoma.^{6,7} Furthermore, sunitinib has been approved for the treatment of imatinib-resistant gastrointestinal stromal tumours (GIST) and sorafenib for advanced hepatocellular carcinoma.^{8,9}

Frequent ADR of sunitinib and sorafenib are hypertension, fatigue, skin abnormalities, gastrointestinal toxicity, and increased risk of bleeding.^{4,5,8–13} However, clinically relevant ADR such as hypothyroidism have been detected in clinical practice, which were not analysed in detail in pivotal trials. Actually, there are several analyses that describe the significance of primary MKI-associated hypothyroidism.^{14–25} This resulted in recommendations by the US Food and Drug Administration (FDA) and the Drug Commission of the German Medical Association in 2006 and 2007, respectively, to assess thyroid function before treatment with sunitinib.^{26–28}

Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib.⁸ The current *Summary of Product Characteristics* (SPC) for sunitinib states a frequency of 2–6% of hypothyroidism observed as an adverse event in phase 3 trials and describes hypothyroidism as ADR as common (1–10%) to very common (>10%).⁸ The current SPC for sorafenib states endocrine disorders such as hypo- and hyperthyroidism as uncommon (affects 1–10 users in 1000).⁹ Several studies report on hypothyroidism under therapy with sorafenib or sunitinib.^{14–25} When analysing the results of these studies, it is necessary to make a difference between thyroid function test abnormalities, subclinical, and clinical hypothyroidism. Thyroid dysfunction means all possible abnormalities of different parameters, e.g. thyroid-stimulating hormone (TSH), free thyroxine (FT4), and triiodothyronine (T3). Subclinical hypothyroidism is defined as a serum TSH-level above the statistically defined upper limit of reference range between 4.5 and 10 mIU/L. Clinical hypothyroidism requiring therapy with a thyroid hormone (TH) (usually levothyroxine) means TSH-values of above 10 mIU/L. The consequences of subclinical thyroid disease (TSH 4.5–10 mIU/L) are minimal and

routine treatment is not recommended.^{29,30} Therefore, clinical hypothyroidism requiring TH therapy should be the primary event of interest.

While alterations of laboratory values like TSH levels have been reported to occur relatively frequently (in 34–85% of patients treated with sunitinib and 10–68% with sorafenib), the rates of symptomatic hypothyroidism requiring treatment ranged from 14–46% for sunitinib and 3–6% for sorafenib.^{14–25} Thus under therapy with sunitinib, the rate of hypothyroidism was uniformly higher than for sorafenib. However, due to the limited numbers of patients (less than 100 in each of these studies) and methodological differences such as setting and follow-up, the variability in incidence of drug-induced hypothyroidism in these studies is substantial. For example, subclinical hypothyroidism occurred in seven of 39 patients (18%) with metastatic renal cell carcinoma during treatment with sorafenib.¹⁹ To the best of our knowledge, no studies are published exploring large, representative databases with regard to sunitinib- or sorafenib-induced hypothyroidism.

2. Objectives

In this large cohort study we analysed, therefore, the incidences of initiating thyroid hormone (TH) therapy as a surrogate for clinical hypothyroidism under sunitinib and sorafenib treatment using claims data for ambulatory prescriptions. Specifically, the following questions are to be answered: First, how many patients have received incident TH prescriptions after starting treatment with sunitinib or sorafenib? Second, is there a difference in risk of treatment with TH between patients treated with sunitinib and sorafenib?

3. Methods

3.1. DAPI database

This study is a retrospective database analysis. The DAPI database comprises anonymous claims data of prescribed drugs dispensed at community pharmacies at the expense of the statutory health insurance (SHI) funds. Roughly 90% of Germany's population is insured by this system. The DAPI data cover more than 80% of all community pharmacies' claims data back to the year 2000.

3.2. Design

We performed a cohort study comparing two treatment groups, i.e. patients initiating therapy with sunitinib or sorafenib. The first prescription of sorafenib or sunitinib between 1st July 2006 and 31st December 2007 constituted the patients' index prescription, respectively. The primary outcome was the first prescription of a TH according to the World Health Organisation

(WHO) Anatomic Therapeutic Chemical (ATC) classification system (code: H03AA) between the index date plus 29 days and the end of the observation period. The prescription of a TH can be seen as a surrogate for clinical hypothyroidism.

Furthermore, patients had to fulfil the following inclusion criteria:

- patients had to be registered in the database for at least 12 months before the index date,
- neither prescription of sunitinib nor sorafenib nor TH in the 12 months before the index date.

Patients were followed until the occurrence of the event (incident TH prescription) or censoring, whichever occurred first. Patients were censored due to the following reasons:

- end of follow up (31st August 2009) without an event: censoring at this date,
- last prescription of any substance in the database, e.g. because of changing the insurance fund, death, or therapy discontinuation: censoring at the time of last prescription,
- interruption of therapy with the MKI defined as a gap of more than 120 days between two prescriptions of MKI: censoring at the time of last prescription of a MKI that appeared before a gap of more than 120 days, plus 120 days,
- discontinuation of therapy of MKI: censoring at the time of last prescription plus 120 days,
- switch of MKI: censoring at the time of first prescription of the other MKI,
- prescription of antithyroid drugs (ATC-code: H03B): censoring at the time of this prescription.

Patients receiving TH or being censored within the first 29 days from the index date were excluded from the primary analysis, as a causal association between the initiation of MKI therapy and hypothyroidism within this short time interval seems unlikely. These patients were however included in a sensitivity analysis where follow-up started from the index date.

The following covariates have been considered as possible confounders:

- year of index prescription: the release of recommendations to monitor thyroid function in patients treated with sunitinib early in 2007²⁸ may have led to an increased awareness of doctors and hence increased case finding in patients starting treatment in 2007 versus 2006.
- medical speciality of prescriber at index date: internal specialist, hospital department, urologist, emergency department, general practitioner, gastroenterologist, and others have been considered, because, depending

on the medical speciality, prescribers may differentially investigate thyroid gland function and detect or treat hypothyroidism.

- region: western or eastern Germany, as there might be differences in prescribing sunitinib or sorafenib and therefore in incidences of hypothyroidism in both parts of Germany.
- insurance membership status: mandatory member, family member, retired person, other, as this variable is a proxy for the demographic variable age or sex in the database.
- type of SHI fund: Allgemeine Ortskrankenkasse (AOK, local health insurance funds), Ersatzkassen (VdAK, substitution health insurance funds), Betriebskrankenkassen (BKK, company health insurance funds), and other.
- number of different ATC3-codes prescribed within 180 days before the index date, as the number of different ATC3-codes is supposed to indicate indirectly the degree of comorbidity.
- drugs affecting thyroid function that have been prescribed within 365 days before the index date, i.e.
 - medicines frequently associated with hypothyroidism according to the SPC or databases of ADRs: amiodarone, bexarotene, interferon alpha-2b/PEG-alpha-2a/PEG-alpha 2b, lithium, octreotide, p-aminosalicylic acid, and ribavirin;
 - antithyroid drugs, as these drugs can induce hypothyroidism as well.
- pre-treatment with imatinib and interferon alpha-2a: interferon alpha-2a is used in renal cell cancer before treatment with sunitinib or sorafenib is initiated, and imatinib is used in GIST before sunitinib. Both drugs may hypothetically also cause disturbances of thyroid function.

3.3. Statistical analyses

Incidence rates (IR) were calculated as the number of cases with incident prescription of TH divided by the sum of follow-up times for sunitinib and sorafenib patients, respectively. Cox proportional hazard models were used to answer the question whether the risk of a prescription of a TH differs between sunitinib and sorafenib patients. The robustness of the results was controlled in sensitivity analyses. We used SPSS version 14.0 for all statistical analyses.

4. Results

4.1. Participants and descriptive data

Six-thousand and four-hundred and forty-four patients who received at least one prescription for

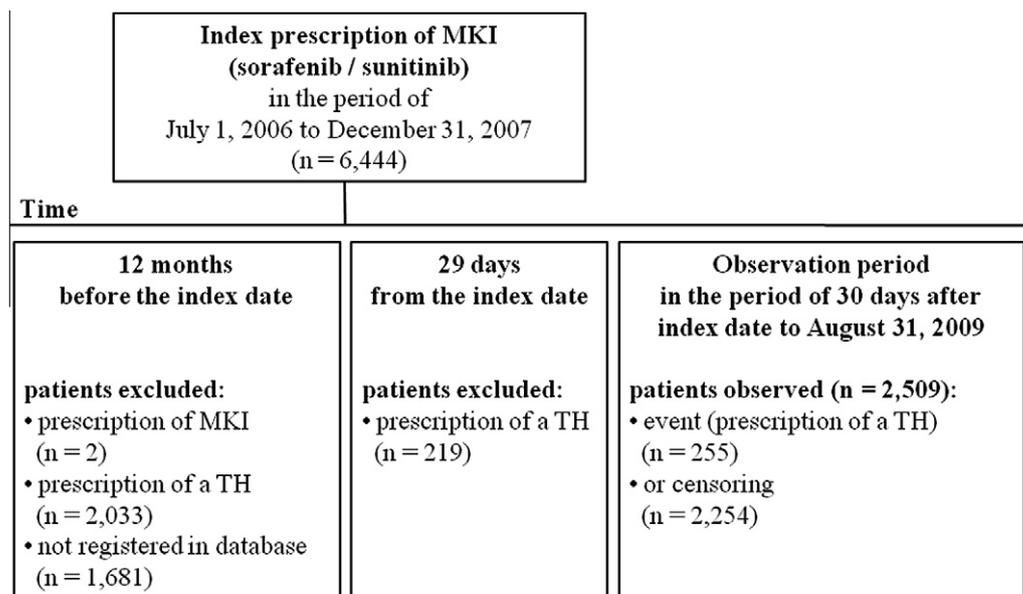


Fig. 1. Study design including inclusion and exclusion criteria and attrition of study cohorts. MKI = multi-kinase inhibitor. TH = thyroid hormone.

sunitinib or sorafenib between 1st July 2006 and 31st December 2007 have been identified. Two patients were excluded because of pre-treatment with any of both MKI. One-thousand and six-hundred and eighty-one patients (26.1%) lacked availability in the database for at least 12 months before the index date. Two-thousand and thirty-three patients (31.5%) were excluded due to treatment with TH in the year before the index date. Furthermore, 219 patients (3.4%) had an event or were censored before the follow-up period started at day 30 after the index date. Finally, 2509 (38.9%) of the patients remained in the study cohort for the primary analysis, of whom 1295 (51.6%) received sunitinib and 1214 (48.4%) sorafenib (see Fig. 1). The characteristics of both cohorts are presented in Table 1. As the substances have been approved in July 2006, the vast majority of index prescriptions were issued in 2007 (70.9%). Sunitinib and sorafenib have mainly been prescribed by internal specialists including oncologists and hospitals, and mostly for retired, hence elderly people. The mean (median) number of further prescribed medicines defined by the number of different ATC3-codes was 12.7 (11) and 13.1 (12), respectively. The proportion of patients pre-treated with interferon alpha-2a was higher for sorafenib (18.2%) than for sunitinib (13.0%). Pre-treatment with imatinib was more frequent in the cohort of sunitinib patients compared to sorafenib (8.2 versus 0.2%; Table 1).

4.2. Results of follow-up

The frequencies of incident TH prescription (= primary event of interest) and reasons for censoring in both groups are presented in Table 2.

Altogether, 255 patients (10.2%) received TH up to the end of the follow-up. The corresponding figures were

178 (13.7%) in the cohort of sunitinib and 77 (6.3%) in sorafenib patients. About half of the patients discontinued therapy both under treatment with sunitinib (50.5%) and sorafenib (54.7%). The IR of thyroid hormone treatment is 24.2 for sunitinib and 12.1 for sorafenib per 100 person-years, respectively. Similar values resulted for different time points in both groups (after a maximum of 90, 180, 365, and 545 days of follow-up, respectively; data not shown).

Fig. 2 shows the Kaplan-Meier curves until occurrence of the event (incident prescription of TH) for both groups.

The unadjusted hazard ratio (HR) for prescription of TH is 2.0 (95% confidence interval (CI) 1.5–2.6) in sunitinib compared to sorafenib patients. The adjusted HR increased to 2.1 (95% CI 1.6–2.7). The covariates ‘prescribed co-medication’ (number of different ATC3-codes, HR: 1.03 [1.02–1.05]), and insurance membership status ‘family member’ (HR: 2.8 [1.7–4.7]) showed a significant influence on the risk of receiving a prescription of TH. Including pre-treatment with imatinib and interferon alpha-2a as covariates into the model did not alter the results.

4.3. Sensitivity analyses

The robustness of the results of the main analysis was confirmed in two sensitivity analyses (Table 3).

- (1) Observation time already started at the index date for all patients. The proportion of patients with the event (i.e. incident prescription of TH) was 13.8% in the sunitinib and 6.6% in the sorafenib group. The unadjusted HR was 1.9 (95% CI 1.5–2.4) and the adjusted HR was 2.0 (1.5–2.6).

Table 1
Characteristics of the study cohort (n = 2509).

	Sunitinib (n = 1295)		Sorafenib (n = 1214)		Proportion of patients with covariate category (%)		Total (%)
	Patients, n		Patients, n		Sunitinib	Sorafenib	
Index year							
2006	306		423		23.6	34.8	29.1
2007	989		791		76.4	65.2	70.9
Prescribing physician							
Internal specialist (including oncologists)	730		577		56.4	47.5	52.1
Hospital	274		372		21.2	30.6	25.8
Urologist	128		98		9.9	8.1	9.0
Emergency department	77		67		5.9	5.5	5.7
General practitioner	38		40		2.9	3.3	3.1
Gastroenterologist	23		33		1.8	2.7	2.2
Other	25		27		1.9	2.2	2.1
Region							
Western Germany	948		891		73.2	73.4	73.3
Eastern Germany	347		323		26.8	26.6	26.7
Insurance membership status							
Retired	890		832		68.7	68.5	68.6
Mandatory member	362		339		28.0	27.9	27.9
Family member	36		34		2.8	2.8	2.8
Other	7		9		0.5	0.7	0.6
Type of SHI fund							
AOK	426		365		32.9	30.1	31.5
VdAK	482		519		37.2	42.8	39.9
BKK	177		159		13.7	13.1	13.4
Other SHI	210		171		16.2	14.1	15.2
Number of medicines prescribed within 180 days before the index date							
ATC3-level; mean (median)	12.7 (11)		13.1 (12)				
Pre-treatment 365 days before index date							
Antithyroids	68		57		5.3	4.7	5.0
Other medicines influencing thyroid gland	49		58		3.8	4.8	4.3
Interferon alfa-2a	168		221		13.0	18.2	15.5
Imatinib	106		2		8.2	0.2	4.3

Abbreviations: AOK = Allgemeine Ortskrankenkassen (local health insurance funds); ATC = Anatomical Therapeutic Chemical classification; BKK = Betriebskrankenkassen (company health insurance funds); SHI = statutory health insurance (funds); VdAK = Ersatzkasse (substitution health insurance funds).

Table 2
Frequencies of incident TH prescription (=primary event of interest) and reasons for censoring.

Event	Sunitinib (n = 1295)	%	Sorafenib (n = 1214)	%	Total (n = 2509)
Prescription of thyroid hormone (=primary event of interest)	178	13.7	77	6.3	10.2
Prescription of antithyroids	35	2.7	42	3.5	3.1
Switch of MKI	179	13.8	206	17.0	15.3
Discontinuation of MKI	654	50.5	664	54.7	52.5
Interruption of MKI	116	9.0	89	7.3	8.2
Dropout of database	92	7.1	112	9.2	8.1
End of follow up (without event or other reason for censoring)	41	3.2	24	2.0	2.6

(2) A time period of 180 days instead of 120 days between two prescriptions was allowed before patients were censored due to interruption of treatment. The proportion of patients with the event (i.e. incident prescription of TH) was 15.5% in the sunitinib and 7.2% in the sorafenib group. The unadjusted HR was 2.0 (95% CI 1.6–2.6) and the adjusted HR 2.1 (1.7–2.8).

5. Discussion

This analysis of large patient cohorts resulted in 6.3% of sorafenib and 13.7% of sunitinib patients receiving incident prescriptions of TH. Incidence rates were 12.1 (sorafenib) and 24.2 (sunitinib) per 100 person-years, respectively. Unadjusted HR for TH therapy was 2.0 for sunitinib compared to sorafenib and remained significant after adjustment for covariates. Hence, patients treated with sunitinib have a two-fold increased risk of requiring TH therapy compared to sorafenib.

We found hypothyroidism in patients treated with sunitinib and sorafenib is a more frequent ADR than mentioned in the European public assessment reports (EPAR) of sunitinib³¹ and sorafenib³² based on available data from pivotal trials. Our results are supported by other, although not fully comparable studies, where the rates of symptomatic hypothyroidism requiring treatment ranged from 14% to 46% for sunitinib and 3% to 6% for sorafenib.^{14–25} Consistent with the EPARs and the other reports, we found higher rates of incident thyroid hormone prescriptions in patients treated with sunitinib versus sorafenib.

The causal mechanism of MKI-induced hypothyroidism is mostly unknown. A (destructive) thyroiditis, inhibition of iodine uptake, alterations in T4/T3 metabolism, increased hepatic type 3 deiodinase activity, marked decrease in thyroid size due to reduced capillary blood flow induced by VEGF receptor (VEGFR) inhibition which results in thyroiditis have been discussed, among others.^{1,21–23,33,34} Both sorafenib and sunitinib inhibit signalling chains that are activated by VEGF, an important regulator of angiogenesis of the thyroid gland, hence one might expect frequencies of hypothyroidism to be similar for sorafenib and sunitinib.³⁵ The

lower incidence of thyroid dysfunction observed in patients treated with sorafenib compared to sunitinib could be related to a differential degree of inhibition of the VEGF receptors (VEGFR-1, -2, -3) by these two drugs. Additionally, the inhibition of kinase activity of certain oncogenes involved in thyroid cells physiology might contribute to the hypothyroidism observed.¹

The proportion of patients pre-treated with interferon alpha-2a was higher for sorafenib than for sunitinib, corresponding with the use of sorafenib as second-line drug after interferon therapy in renal cell carcinoma.⁹ Pre-treatment with imatinib was more frequent in the cohort of sunitinib patients compared to sorafenib which relates to the use of sunitinib in patients with GIST after failure of imatinib treatment.⁸ However, including both pre-treatments as covariates into the model did not change the risk for receiving TH prescriptions. This may be explained by the fact that the occurrence of the ADR hypothyroidism is unrelated to the indication (i.e. type of cancer) for which the drugs are used.

5.1. Limitations

Any analyses using TH replacement as a surrogate, or even just clinically detected hypothyroidism, is subject to underestimate the true prevalence of hypothyroidism due to low case finding resulting from subtle symptoms or misdiagnoses, etc. A further, although small underestimation of incidence of hypothyroidism can be expected in our analyses, as the prescription might be filled in a pharmacy not covered by our database or the prescription is not filled in a pharmacy at all. Furthermore, medication supplies during periods of hospitalisation or staying abroad are not detected. Therefore, the number of events may be misclassified in some cases. However, in the first scenario we would expect misclassification to be non-differential as the coverage of pharmacies should be unrelated to the type of therapy a patient receives, i.e. sunitinib or sorafenib. In the latter scenario, differences in periods of hospitalisation between sunitinib and sorafenib can lead to a bias in the HR. This problem was minimised by censoring patients with interruptions of their MKI therapy exceeding 120 or 180 days in a sensitivity analysis which did not alter the results.

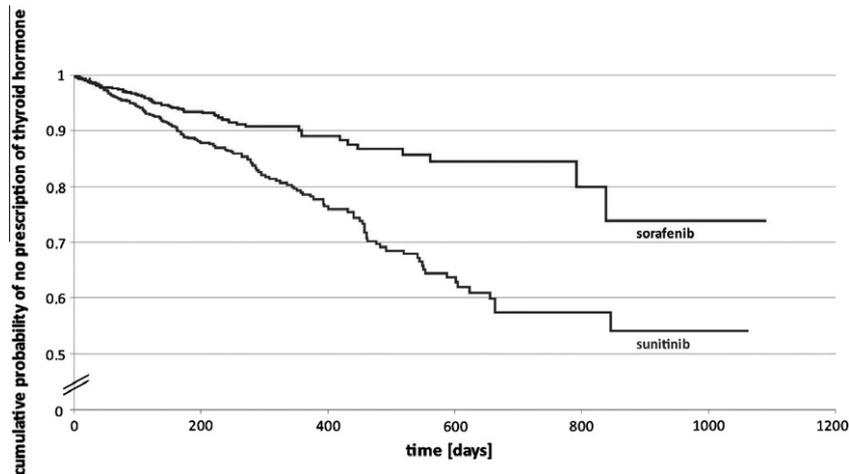


Fig. 2. Kaplan–Meier curves showing cumulative probabilities of being free of event (i.e. no prescription of a thyroid hormone). The upper line represents sorafenib, the lower line sunitinib patients (due to clarity of presentation, crosses for censored cases are not displayed).

Table 3
Results of the two sensitivity analyses in comparison to the main analysis.

	Patients, <i>n</i>		Unadjusted HR		Adjusted HR	
	Sunitinib	Sorafenib	HR	95% CI	HR	95% CI
Main analysis	1295	1214	2.0	1.5–2.6	2.1	1.6–2.7
Sensitivity analyses						
(1)	1400	1328	1.9	1.5–2.4	2.0	1.5–2.6
(2)	1295	1214	2.0	1.6–2.6	2.1	1.7–2.8

Abbreviations: CI = confidence interval; HR = hazard ratio.

Furthermore, data on indication or dosage and further confounders such as age, sex, or baseline TSH value are not available in our database. Therefore, residual bias from unmeasured confounding cannot be excluded.

5.2. Advantages

The study cohort can be regarded as representative for the SHI system covering roughly 90% of the German population. Thus, external validity is assumed. The database allows for inclusion of a large number if not nearly all ambulatory patients, in spite of strict inclusion and exclusion criteria. The large study size is an advantage, especially for the question investigated, as sunitinib and sorafenib are used only relatively rarely, and clinical trials may investigate small numbers of patients only.

6. Conclusions and recommendations for clinicians

Our data support the recent finding that published reports of pivotal randomised controlled trials and initial drug labels contain limited information about serious ADRs of targeted anticancer drugs.³⁶ It is important to measure thyroid function both at baseline and throughout treatment with sunitinib and sorafenib, given the notable incidence and severity of thyroid function abnormalities during treatment with these

drugs.^{8,9,13,28,33,37–40} Caution should be taken, however, in prescribing TH for cancer patients with only slightly increased serum-TSH level not presenting any symptoms. If clinical hypothyroidism occurs, it can be treated with TH which leads to fast and complete correction of increased TSH values and should not restrict the use of sunitinib and sorafenib in malignant diseases in general.²⁴

Conflict of interest statement

None declared.

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